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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/00 A2

(11) International Publication Number: WO 00/64420

(43) International Publication Date: 2 November 2000 (02.11.00)

(21) International Application Number: PCT/CA00/00494

(22) International Filing Date: 28 April 2000 (28.04.00)

(30) Priority Data:

60/131,464	28 April 1999 (28.04.99)	US
60/135,545	24 May 1999 (24.05.99)	US
60/143,123	9 July 1999 (09.07.99)	US

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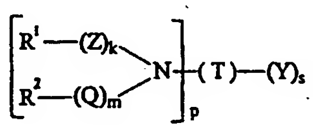
(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: COMPOSITIONS AND METHODS FOR TREATING AMYLOIDOSIS



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(57) Abstract

Therapeutic compounds and methods for modulating amyloid aggregation in a subject, whatever its clinical setting, are described. Amyloid aggregation is modulated by the administration to a subject of an effective amount of a therapeutic compound of formula (1) or a pharmaceutically acceptable salt or ester, such that modulation of amyloid aggregation occurs. R^1 and R^2 are each independently a hydrogen atom or a substituted or unsubstituted aliphatic or aryl group. Z and Q are each independently a carbonyl (C=O), thiocarbonyl (C=S), sulfonyl (SO_2), or sulfoxide (S=O) group. "k" and "m" are 0 or 1, provided when k is 1, R^1 is not a hydrogen atom, and when m is 1, R^2 is not a hydrogen atom. In an embodiment, at least one of k or m must equal 1. "p" and "s" are each independently positive integers selected such that the biodistribution of the therapeutic compound for an intended target site is not prevented while maintaining activity of the therapeutic compound. T is a linking group and Y is a group of the formula: –A X, wherein A is an anionic group at physiological pH, and X is a cationic group.

COMPOSITIONS AND METHODS FOR TREATING AMYLOIDOSIS

RELATED APPLICATIONS

This application claims the benefit of priority under 35 U.S.C. 119(e) to copending U.S. Provisional Application No. 60/131,464, filed on April 28, 1999, U.S. Provisional Application No. 60/135,545, filed on May 24, 1999, and U.S. Provisional Application No. 60/143,123, filed on July 9, 1999, the entire contents of which are incorporated herein by reference. This application is also related to U.S. Patent No. 5972328, issued October 26, 1999, the entire contents of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Amyloidosis refers to a pathological condition characterized by the presence of amyloid. "Amyloid" is a generic term referring to a group of diverse but specific extracellular protein deposits which are seen in a number of different diseases. Though diverse in their occurrence, all amyloid aggregates have common morphologic properties, stain with specific dyes (e.g., Congo red), and have a characteristic red-green birefringent appearance in polarized light after staining. They also share common ultrastructural features and common x-ray diffraction and infrared spectra.

Amyloidosis can be classified clinically as primary, secondary, familial and/or isolated. Primary amyloidosis appears *de novo* without any preceding disorder. Secondary amyloidosis is that form which appears as a complication of a previously existing disorder. Familial amyloidosis is a genetically inherited form found in particular geographic populations. Isolated forms of amyloidosis are those that tend to involve a single organ system. Different amyloids are also characterized by the type of protein present in the aggregate. For example, neurodegenerative diseases such as scrapie, bovine spongiform encephalitis, Creutzfeldt-Jakob disease, transmissible spongiform encephalitis ("TSE"), and the like are characterized by the appearance and accumulation of a protease-resistant form of a prion protein (referred to as AScr or PrP-27) in the central nervous system.

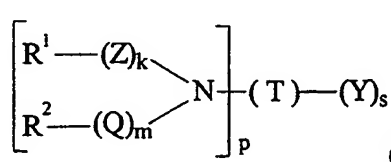
Similarly, Alzheimer's disease, another neurodegenerative disorder, is characterized by congophilic angiopathy, neuritic plaques and neurofibrillary tangles, all of which have the characteristics of amyloids. In this case, the plaques and blood vessel amyloid are formed by the beta protein. Other systemic diseases such as adult-onset diabetes, complications of long-term hemodialysis and sequelae of long-standing inflammation or plasma cell dyscrasias are characterized by the accumulation of amyloids systemically. In each of these cases, a different amyloidogenic protein is involved.

Other harmful effect of amyloidosis include toxicity to cells by the presence of greater than normal levels of amyloid *in vivo*. It has been noted that once amyloid fibrils are assembled into fibers, e.g., amyloid aggregation, the fibers are known to be toxic to nerve cells and present a risk to the viability of those cells. So in addition to the noted detrimental effects of amyloid plaques *in vivo*, the presence of amyloid itself can be harmful to the organism.

SUMMARY OF THE INVENTION

The present invention provides methods and compositions which are useful in the treatment of amyloidosis. In particular, methods and compositions are disclosed for inhibiting, preventing and treating amyloid aggregation, e.g., in pancreatic islets wherein the amyloidotic aggregates to be treated are, in an embodiment, islet amyloid polypeptide (IAPP)-associated amyloid aggregates, e.g., having at least some β-sheet structure. Accordingly, the compositions and methods of the invention are useful for inhibiting amyloidosis in disorders in which such amyloid aggregation occurs.

In one embodiment, a method of the invention involves administering *in vivo* or *ex vivo* an effective amount of a therapeutic compound having the formula (i):



(i)

or a pharmaceutically acceptable salt or ester, such that modulation of amyloid aggregation occurs. R^1 and R^2 are each independently a hydrogen atom or a substituted or unsubstituted aliphatic or aryl group. Z and Q are each independently a carbonyl (C=O), thiocarbonyl (C=S), sulfonyl (SO_2), or sulfoxide (S=O) group. "k" and "m" are 0 or 1, provided when k is 1, R^1 is not a hydrogen atom, and when m is 1, R^2 is not a hydrogen atom. In an embodiment, at least one of k or m must equal 1. "p" and "s" are each independently positive integers selected such that the biodistribution of the therapeutic compound for an intended target site is not prevented while maintaining activity of the therapeutic compound. T is a linking group and Y is a group of the formula —AX, wherein A is an anionic group at physiological pH, and X is a cationic group. Linking group T is in some cases advantageously of the formula $-(CD^1D^2)_n-$, wherein n is an integer from 1 to 25, C is carbon and D^1 and D^2 are independently hydrogen or halogen atoms; aliphatic, aromatic or heterocyclic groups; alkylamino or arylamino; or alkyloxy or aryloxy. In a preferred embodiment, the therapeutic compounds disclosed herein prevent or inhibit amyloid aggregation.

The methods of the invention involve, in an embodiment, administering to a subject a therapeutic compound which inhibits, reduces or disrupts amyloid deposits, e.g., IAPP-associated amyloid deposits.

In a preferred embodiment, therapeutic compounds in accordance with the present disclosure include those where R^1 is an alkyl, alkenyl, or aryl group, k is one, Z is a carbonyl group, R^2 is a hydrogen atom or an alkyl group, m is zero, p and s are 1, T is an alkylene group, and Y is SO_3X wherein X is H^+ or other cation such as cations of alkali metals. In another embodiment a group of therapeutic compounds include those where R^1 and R^2 are alkyl, alkenyl, or aryl groups, or R^1 and R^2 are taken together to form an alkylene group, k and m are each one, Z and Q are carbonyl groups, p and s are 1, T is an alkylene group, and Y is SO_3X where X is H^+ or other cation such as cations of alkali metals.

In an further preferred embodiment, therapeutic compounds in accordance with the present disclosure include those where R^1 is an alkyl, alkenyl, or aryl

group, k and m are zero, R^2 is hydrogen or an alkyl group, p and s are each one, T is an alkylene group, and Y is SO_3X, wherein X is H^+ or another cation, such as alkali metal cations. In another embodiment, therapeutic compounds include those where R^1 and R^2 are alkyl, alkenyl, or aryl groups, or R^1 and R^2 are taken together to form an alkylene group, k and m are zero, p and s are each one, T is an alkylene group, Y is SO_3X, where X is H^+ or another cation, such as alkali metal cations.

The therapeutic compounds disclosed herein are administered to a subject by a route which is effective for modulation of amyloid aggregation. Suitable routes of administration include subcutaneous, intravenous and intraperitoneal injection. The therapeutic compounds of the invention have been found to be effective when administered orally. Accordingly, a preferred route of administration is oral administration. The therapeutic compounds can be administered with a pharmaceutically acceptable vehicle.

Methods are also disclosed herein for treating a disease state associated with amyloidosis by administering to a subject an effective amount of a therapeutic compound having the formula described *supra*, such that a disease state associated with amyloidosis is treated.

The invention further provides pharmaceutical compositions for treating amyloidosis. The pharmaceutical compositions include a therapeutic compound of the invention in an amount effective to modulate amyloid aggregation and a pharmaceutically acceptable vehicle.

The invention also provides packaged pharmaceutical compositions for treating amyloidosis. The packaged pharmaceutical compositions include a therapeutic compound of the invention and instructions for using the pharmaceutical composition for treatment of amyloidosis.

BRIEF DESCRIPTION OF THE DRAWING

Figures 1-9 depict exemplary chemical structures of compounds described in the specification.

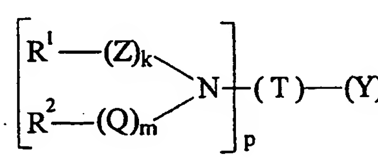
Figure 10 is the ^{1}H NMR spectrum of 8-methoxy-5-quinolinesulfonic acid, sodium salt (in DMSO-d_6), made as in Example 9.

Figures 11 and 12 are histograms showing the effectiveness of compounds of the invention, **XXVII** and **XVII**, respectively in an acute animal model for secondary amyloidosis, in accordance with Example 5.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure pertains to methods and compositions useful for treating amyloidosis. The disclosed methods involve administering to a subject a therapeutic compound which modulates amyloid aggregation. "Modulation of amyloid aggregation" is intended to encompass prevention or stopping of amyloid formation, inhibition or slowing down of further amyloid aggregation in a subject with ongoing amyloidosis, e.g., already having amyloid aggregates, and reducing or reversing of amyloid aggregates in a subject with ongoing amyloidosis. Modulation of amyloid aggregation is determined relative to an untreated subject or relative to the treated subject prior to treatment. "Amyloid" includes IAPP-associated amyloid, including, but not limited to, β-sheet amyloid assembled substantially from IAPP subunits as well as other types f amyloid-related diseases such as Alzheimer's Disease and systemic amyloid disorders.

In one embodiment, a method in accordance with the invention includes administering to the subject an effective amount of a therapeutic compound which has at least one anionic group covalently attached to a linking group. The therapeutic compound has the formula **(i)**:



(i)

or a pharmaceutically acceptable salt or ester thereof. R^1 and R^2 are each independently a hydrogen atom or a substituted or unsubstituted aliphatic or aryl group. Z and Q are each independently a carbonyl (C=O), thiocarbonyl (C=S), sulfonyl (SO_2), or sulfoxide (S=O) group. "k" and "m" are 0 or 1, provided when k

is 1, R^1 is not a hydrogen atom, and when m is 1, R^2 is not a hydrogen atom. In an embodiment, at least one of k or m must equal 1. "p" and "s" are each independently positive integers selected such that the biodistribution of the therapeutic compound for an intended target site is not prevented while maintaining activity of the therapeutic compound. T is a linking group and Y is a group of the formula —AX, wherein A is an anionic group at physiological pH, and X is a cationic group. Linking group T is, in some cases, advantageously of the formula $-(CD^1D^2)_n-$, wherein n is an integer from 1 to 25, C is carbon and D^1 and D^2 are independently hydrogen or halogen atoms; aliphatic, aromatic or heterocyclic groups; alkylamino or arylamino; or alkyloxy or aryloxy. In a preferred embodiment, the therapeutic compounds disclosed herein prevent or inhibit amyloid protein assembly into insoluble fibrils which, *in vivo*, are deposited in various organs. It is also believed, without limitation, that the compounds also prevent the amyloid protein, whether in soluble or non-soluble form, from binding or adhering to a cell surface and causing cell damage or toxicity.

The number of amino or amido groups and anionic groups (i.e., determined by "p" and "s") are each independently selected such that the biodistribution of the compound for an intended target site is not prevented while maintaining activity of the compound. Further, p and s are selected such that a sufficient number of groups, Z, Q, T and/or Y, are presented for treatment of a disease or condition. For example, the number of anionic groups is not so great as to inhibit traversal of an anatomical barrier, such as a cell membrane, or entry across a physiological barrier, such as the blood-brain barrier, in situations where such properties are desired. The integers for p and s are preferably about 1 to about 10. The values intermediate to those listed also are intended to be part of this invention, e.g., about 1 to 9, about 1 to 8, about 1 to 7, about 1 to 6, about 1 to 5, about 1 to 4, about 1 to 3, and about 1 to 2. For example, ranges of p and s using a combination of any of the above values recited as upper and/or lower limited are intended to be included. In one embodiment, p and s are integers between and including 1 and 5. In another embodiment, p and s are integers between and including 3 and 8. Linking group T is in some cases advantageously of the formula $-(CD^1D^2)_n-$, wherein n is an integer

from 1 to 25, C is carbon and D^1 and D^2 are independently hydrogen or halogen atoms; aliphatic, aromatic or heterocyclic groups; alkylamino or arylamino; or alkyloxy or aryloxy.

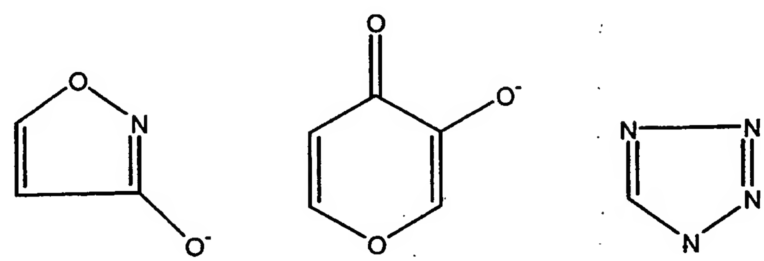
In an embodiment, a group of therapeutic compounds include those where R^1 is an alkyl, alkenyl, or aryl group, k is one, Z is a carbonyl group, R^2 is a hydrogen atom or an alkyl group, m is zero, p and s are 1, T is an alkylene group, and Y is SO_3X wherein X is H^+ or another cation, such as alkali metal cations. In another embodiment a group of therapeutic compounds include those where R^1 and R^2 are alkyl, alkenyl, or aryl groups, or R^1 and R^2 are taken together to form an alkylene group, k and m are each one, Z and Q are carbonyl groups, p and s are 1, T is an alkylene group, and Y is SO_3X where X is H^+ or another cation, such as alkali metal cations.

In another embodiment a group of therapeutic compounds include those where R^1 is an alkyl, alkenyl, or aryl group, k and m are zero, R^2 is hydrogen or an alkyl group, p and s are each one, T is an alkylene group, and Y is SO_3X wherein X is H^+ or another cation, such as alkali metal cations. In another embodiment, a group of therapeutic compounds include those where R^1 and R^2 are alkyl, alkenyl, or aryl groups, or R^1 and R^2 are taken together to form an alkylene group, k and m are zero, p and s are each one, T is an alkylene group, Y is SO_3X where X is H^+ or another cation, such as alkali metal cations.

Not intending to be bound by theory, it is believed that under physiological conditions it is preferable that the nitrogen of the therapeutic compound is converted into an ammonium salt. In keeping with this theory, it is believed that acetylated nitrogens are hydrolyzed by an enzyme and converted into a positively charged ammonium group under normal physiological conditions. Likewise, in cases where the amine nitrogen is dialkylated, it is believed that the nitrogen is converted into an ammonium group by enzymatic activity. It is further believed that these conversions better enable the therapeutic compounds of the invention to interact with amyloid aggregates and/or amyloid precursors, e.g., cross the blood

brain barrier, cross membranes, solubilize, etc., under physiological conditions *in vivo*.

For purposes of the present disclosure, the anionic group is negatively charged at physiological pH. Preferably, the anionic group is a sulfonate group or a functional equivalent thereof. "Functional equivalents" of sulfonates are intended to include compounds such as sulfamates as well as bioisosteres. Bioisosteres encompass both classical bioisosteric equivalents and non-classical bioisosteric equivalents. Classical and non-classical bioisosteres of sulfate and sulfonate groups are known in the art (see e.g. Silverman, R.B. *The Organic Chemistry of Drug Design and Drug Action*, Academic Press, Inc.: San Diego, CA, 1992, pp. 19-23). Accordingly, a therapeutic compound of the invention can comprise at least one anionic group including sulfonates, sulfates, sulfamates, phosphonates, phosphates, carboxylates, and heterocyclic groups of the following formulae:



A therapeutic compound of the invention typically further comprises a counter cation (i.e., X^+ in formula (i)). Cationic groups include positively charged atoms and moieties. If the cationic group is hydrogen, H^+, then the compound is considered an acid, e.g., 3-acetylamino-1-propanesulfonic acid. If hydrogen is replaced by a metal or its equivalent, the compound is a salt of the acid. Pharmaceutically acceptable salts of the therapeutic compound are within the scope of the invention. For example, X^+ can be a pharmaceutically acceptable alkali or alkaline earth metal, polycationic counter ion or ammonium. A preferred pharmaceutically acceptable salt is a sodium salt but other salts are also contemplated within their pharmaceutically acceptable range.

Within the therapeutic compound, the Y group(s) is covalently attached to a linking group T. Linking group T is advantageously of the formula $-(CD^1D^2)_n-$, wherein n is an integer from 1 to 25, C is carbon and D^1 and D^2 are independently hydrogen or halogen atoms; aliphatic, aromatic or heterocyclic groups; alkylamino or arylamino; or alkyloxy or aryloxy. As such, T may be a carbohydrate, polymer, peptide or peptide derivative, aliphatic group, alicyclic group, heterocyclic group, aromatic group or combinations thereof, and may further be substituted with, e.g., one or more amino, nitro, halogen, thiol or hydroxy groups.

As used herein, the term "carbohydrate" is intended to include substituted and unsubstituted mono-, oligo-, and polysaccharides. Monosaccharides are simple sugars usually of the formula $C_6H_{12}O_6$ that can be linked to form oligosaccharides or polysaccharides. Monosaccharides include enantiomers and both the d and l stereoisomers of monosaccharides. Carbohydrates can have multiple anionic groups attached to each monosaccharide moiety. For example, in sucrose octasulfate, four sulfate groups are attached to each of the two monosaccharide moieties.

As used herein, the term "polymer" is intended to include molecules formed by the chemical union of two or more combining subunits called monomers. Monomers are molecules or compounds which usually contain carbon and are of relatively low molecular weight and simple structure. A monomer can be converted to a polymer by combination with itself or other similar molecules or compounds. A polymer may be composed of a single identical repeating subunit or multiple different repeating subunits (copolymers).

The term "peptide" includes two or more amino acids covalently attached through an amide bond. Amino acids include those naturally occurring amino acids found in proteins such as glycine, alanine, valine, cysteine, leucine, isoleucine, serine, threonine, methionine, glutamic acid, aspartic acid, glutamine, asparagine, lysine, arginine, proline, histidine, phenylalanine, tyrosine, and tryptophan. The term amino acid further includes analogs, derivatives and congeners of naturally occurring amino acids, one or more of which can be present

in a peptide derivative. For example, amino acid analogs can have lengthened or shortened side chains or variant side chains with appropriate functional groups. Also included are the D and L stereoisomers of an amino acid when the structure of the amino acid admits of stereoisomeric forms. The term "peptide derivative" further includes compounds which contain chemical fragments which mimic a peptide backbone but are not amino acids (so-called peptidomimetics), such as benzodiazepine molecules (see e.g. James, G. L. et al. (1993) *Science* 260:1937-1942). The anionic groups can be attached to a peptide or peptide derivative through a functional group on the side chain of certain amino acids or other suitable functional group. For example, a sulfate or sulfonate group can be attached through the hydroxy group in the side chain of a serine residue. A peptide can be designed to interact with a binding site for a basement membrane constituent (e.g., HSPG) in an amyloidogenic protein (as described above).

The term "aliphatic group" is intended to include organic groups characterized by straight or branched chains, typically having between 1 and 22 carbon atoms. Aliphatic groups include alkyl groups, alkenyl groups and alkynyl groups. In complex structures, the chains can be branched or cross-linked. Alkyl groups include saturated hydrocarbons having one or more carbon atoms, including straight-chain alkyl groups and branched-chain alkyl groups. Such hydrocarbon moieties may be substituted on one or more carbons with, for example, a halogen, a hydroxyl, a thiol, an amino, an alkoxy, an alkylcarboxy, an alkylthio, or a nitro group. Unless the number of carbons is otherwise specified, "lower aliphatic" as used herein means an aliphatic group, as defined above (e.g., lower alkyl, lower alkenyl, lower alkynyl), but having from one to six carbon atoms. Representative of such lower aliphatic groups, e.g., lower alkyl groups, are methyl, ethyl, n-propyl, isopropyl, 2-chloropropyl, n-butyl, sec-butyl, 2-aminobutyl, isobutyl, tert-butyl, 3-thiopentyl, and the like. As used herein, the term "amino" means a $-NH_2$; the term "nitro" means $-NO_2$; the term "halogen" designates -F, -Cl, -Br or -I; the term "thiol" means a -SH; and the term "hydroxyl" means -OH. Thus, the term "alkylamino" as used herein means a -NHR, in which R is an alkyl group as defined above.. The term "alkylthio" refers to a –SR, in which R is an alkyl group

as defined above. The term "alkylcarboxyl" means a $-CO_2R$, in which R is an alkyl group as defined above. The term "alkoxy" as used herein means a –OR, in which R is an alkyl group as defined above. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like. The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous to alkyls, but which contain at least one double or triple bond respectively.

The term "alicyclic group" is intended to include closed ring structures of three or more carbon atoms. Alicyclic groups include cycloparaffins or naphthenes which are saturated cyclic hydrocarbons, cycloolefins which are unsaturated with two or more double bonds, and cycloacetylenes which have a triple bond. They do not include aromatic groups. Examples of cycloparaffins include cyclopropane, cyclohexane, and cyclopentane. Examples of cycloolefins include cyclopentadiene and cyclooctatetraene. Alicyclic groups also include fused ring structures and substituted alicyclic groups such as alkyl substituted alicyclic groups. In the instance of the alicyclics such substituents can further comprise a lower alkyl, a lower alkenyl, a lower alkoxy, a lower alkylthio, a lower alkylamino, a lower alkylcarboxyl, a nitro, a hydroxyl, $-CF_3$, -CN, or the like.

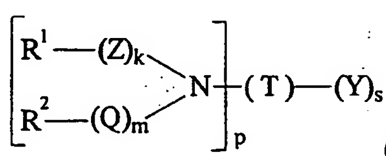
The term "heterocyclic group" is intended to include closed ring structures in which one or more of the atoms in the ring is an element other than carbon, for example, nitrogen, or oxygen. Heterocyclic groups can be saturated or unsaturated and heterocyclic groups such as pyrrole and furan can have aromatic character. They include fused ring structures such as quinoline and isoquinoline. Other examples of heterocyclic groups include pyridine and purine. Heterocyclic groups can also be substituted at one or more constituent atoms with, for example, a halogen, a lower alkyl, a lower alkenyl, a lower alkoxy, a lower alkylthio, a lower alkylamino, a lower alkylcarboxyl, a nitro, a hydroxyl, $-CF_3$, -CN, or the like.

The term "aromatic group" is intended to include unsaturated cyclic hydrocarbons containing one or more rings. Aromatic groups include 5- and 6-membered single-ring groups which may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole,

triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. The aromatic ring may be substituted at one or more ring positions with, for example, a halogen, a lower alkyl, a lower alkenyl, a lower alkoxy, a lower alkylthio, a lower alkylamino, a lower alkylcarboxyl, a nitro, a hydroxyl, $-CF_3$, -CN, or the like.

The therapeutic compound of the invention can be administered in a pharmaceutically acceptable vehicle. As used herein "pharmaceutically acceptable vehicle" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like which are compatible with the activity of the compound and are physiologically acceptable to the subject. An example of a pharmaceutically acceptable vehicle is buffered normal saline (0.15 molar NaCl). The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the therapeutic compound, use thereof in the compositions suitable for pharmaceutical administration is contemplated. Supplementary active compounds can also be incorporated into the compositions.

In a preferred embodiment of the method of the invention, the therapeutic compound administered to the subject is of formula (i):

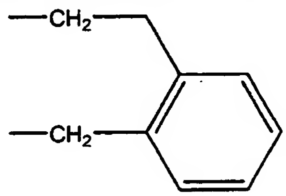


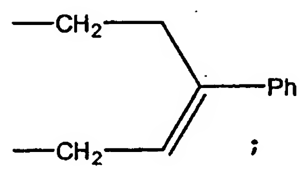
(i)

or a pharmaceutically acceptable salt or ester thereof. R^1 and R^2 are each independently a hydrogen atom or a substituted or unsubstituted aliphatic or aryl group. Z and Q are each independently a carbonyl (C=O), thiocarbonyl (C=S), sulfonyl (SO_2), or sulfoxide (S=O) group. "k" and "m" are 0 or 1, provided when k is 1, R^1 is not a hydrogen atom, and when m is 1, R^2 is not a hydrogen atom. In an embodiment, at least one of k or m must equal 1. "p" and "s" are each independently positive integers selected such that the biodistribution of the therapeutic compound for an intended target site is not prevented while

maintaining activity of the therapeutic compound. T is a linking group and Y is a group of the formula —AX, wherein A is an anionic group at physiological pH, and X is a cationic group.

In an embodiment, "k" and "m" are both 0, and R^1 and R^2, taken together with the nitrogen to which they are attached, form an unsubstituted or substituted heterocycle, preferred groups include





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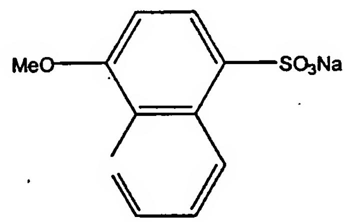


Preferred therapeutic compounds include 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid **(LVX)**; DL-2-amino-5-phosphovaleric acid **(LVIII)**; 1,2,3,4-tetrahydroisoquinoline, hydrochloride **(LVIX)**; 4-Phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine **(LVXV)**; cyclohexylsulfamic acid **(LVXI)**; *O*-phospho-*L*-serine **(LVXII)**;; 8-methoxyquinoline-5-sulfonic acid **(LVXIV)**; 3-amino-2-hydroxy-1-propanesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid **(LVXVII)**, and pharmaceutically acceptable salts thereof.

In an embodiment, therapeutic compounds include those where R^1 is an alkyl, an alkenyl, or an aryl group, k is one, Z is a carbonyl group, R^2 is a hydrogen atom or an alkylene group, m is zero, p and s are 1, T is an alkylene group, and Y is SO_3X wherein X is H^+ or another cation, such as alkali metal cations. Specific examples include mono-*N*-acylated compounds (e.g., R^1 is an alkyl, an alkenyl, or an aryl group, R^2 is a hydrogen atom or an alkyl group) such as 3-acetylamino-1-propanesulfonic acid **(VIII)**, 2-acrylamido-2-methyl-1-propanesulfonic acid

(XXI), and 3-benzoylamino-1-propanesulfonic acid (X). In another embodiment, a group of therapeutic compounds include those where R^1 and R^2 are alkyl, alkenyl, or aryl, or R^1 and R^2 are linked together to form an alkylene group, k and m are each one, Z and Q are each independently a carbonyl or a sulfonyl group, p and s are 1, T is an alkylene group, and Y is SO_3X where X is H^+ or another cation, such as alkali metal cations. Specific examples include di-*N*-acylated compounds (including heterocyclic compounds, e.g., R^1 and R^2 are taken together to form an alkylene group) such as 3-phthalimido-1-propanesulfonic acid (XXIII), N-(3-sulfopropyl)saccharin sodium salt (XXV), and 4-phthalimido-1-butanesulfonic acid (XIX). In an advantageous embodiment, T is propylene or butylene.

In an embodiment a group of therapeutic compounds include those where R^1 is an alkyl, alkenyl, or aryl group, k and m are zero, R^2 is hydrogen or an alkyl group, or R^1 and R^2 are taken together to form an alkylene or an alkenylene group, p and s are each one, T is an alkylene group, and Y is SO_3X wherein X is H^+ or another cation, such as alkali metal cations. Specific examples include mono-*N*-alkylated or arylated compounds such as 3-phenylamino-1-propanesulfonic acid sodium salt (XIII), 3-(4-pyridylamino)]-1-propanesulfonic acid (XII), 3-(benzylamino)-1-propanesulfonic acid (XV), 2-deoxy-2-(3-sulfopropyl)amino-d-glucose (XX), 1-phenyl-2,3,-dimethyl-4-methylamino-pyrazolon-5-*N*-methylsulfonic acid (XXVII), 3-[(-3,5-dimethyl-1-adamantyl)-amino]-1-propanesulfonic acid (XXIV), 3-(2-hydroxyethyl)amino-1-propanesulfonic acid (XXX), 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid (XXXII), (-)-3-[(*R*)-2-hydroxy-1-propyl]amino-1-propanesulfonic acid (XXXIV), 3-[(*d,l*)-2-hydroxy-1-propyl]-1-propanesulfonic acid (XXXV), 3-(4-hydroxy-1-butyl)amino-1-propanesulfonic acid (XXXVI), 3-(5-hydrox-1-pentyl)amino-1-propanesulfonic acid (XXXI), 3-(6-hydroxy-1-hexyl)amino-1-propanesulfonic acid (XXXIII), 3-(4-hydroxyphenyl)amino-1-propanesulfonic acid (XXXV), (+)-3-[(*S*)-2-hydroxy-1-propyl]amino-1-propanesulfonic acid (XXXVII), (+)-3-[(*S*)-1-hydroxy-2-propyl]amino-1-propanesulfonic acid (XXXIX), (-)-3-[(*R*)-1-hydroxy-2-propyl]amino-1-propanesulfonic acid (XL), (+)-3-[(*S*)-1-hydroxy-2-butyl]amino-1-propanesulfonic acid (XLIII), (-)-3-[(*R*)-1-hydroxy-2-butyl]amino-1-

propanesulfonic acid (**XLIV**), 3-[(*dl*)-5-hydroxy-2-pentyl]amino-1-propanesulfonic acid (**XXXVIII**), 3-[(*dl*)-6-hydroxy-2-hexyl]amino-1-propanesulfonic acid (**XLI**), 3-(1-hydroxymethyl-1-cyclopentyl)amino-1-propanesulfonic acid (**XLII**), 3-amylamino-1-propanesulfonic acid (**XLV**), 3-hexylamino-1-propanesulfonic acid (**XLVII**), 3-heptylamino-1-propanesulfonic acid (**XLVIII**), 3-octylamino-1-propanesulfonic acid (**XLIX**), 3-nonylamino-1-propanesulfonic acid (**L**), 3-decylamino-1-propanesulfonic acid (**LI**), 3-undecylamino-1-propanesulfonic acid (**LII**), 3-dodecylamino-1-propanesulfonic acid (**LIII**), 3-tridecylamino-1-propanesulfonic acid (**LIV**), 3-tetradecylamino-1-propanesulfonic acid (**LV**), 3-hexadecylamino-1-propanesulfonic acid (**LVI**), 3-octadecylamino-1-propanesulfonic acid (**LVII**), dimethyl(3-sulfopropyl)-tetradecylammonium hydroxide, inner salt (**LVXVIII**), and 2-(3-Sulfobutyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-b] indole, sodium salt (**LVXIX**). In another embodiment a group of therapeutic compounds include those where R^1 and R^2 are alkyl, alkenyl, or aryl groups, or R^1 and R^2 are taken together to form an alkylene group, k and m are zero, p and s are each one, T is an alkylene group, Y is SO_3X where X is H^+ or other cation such as cations of alkali metals. Specific examples include di-*N*-alkylated compounds (including heterocyclic compounds, e.g., R^1 and R^2 are alkylene) such as 3-dimethylamino-1-propanesulfonic acid (**XI**), 4-(1-piperidinyl)-1-ethanesulfonic acid (**XIV**), 3-[1-(1,2,3,6-tetrahydropyridyl)]-1-propanesulfonic acid (**XVI**), 3-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid (**XVII**), 3-[2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid (**I**), 3-[1-(1,2,3,4-tetrahydroquinolinyl)]-1-propanesulfonic acid (**III**), 2-(3-sulfopropyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole, sodium salt (**V**), 3-(1-indolinyl)-1-propanesulfonic acid (**VII**), 3-[2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid (**IX**), 3-(2-isoindolinyl)-1-propanesulfonic acid (**II**), 2-(3-sulfopropyl)-(*S*)-nicotinium hydroxide inner salt (**IV**), 3-(4-benzyl-1-piperidinyl)-1-propanesulfonic acid (**VI**), 3-[2-(1,2,3,4,5,6,7,8-octahydroisoquinolinyl)]-1-propanesulfonic acid (**XVIII**), Thiazol Yellow G (**XXVIII**), 3-sulfonylmethylphenylalanine (**XXII**), Chicago Sky Blue 6B (**XXIX**), 4-[2-(1,2,3,4-

tetrahydroisoquinolinyl)]-1-butanesulfonic acid **(XXVI)**, and 3-Sulfomethyl-L-phenylalanine **(LVXIII)**.

R^1 may be a lower alkyl group, R^2 a lower alkyl group and T a lower alkylene group. Preferably, R^1 is a methyl, ethyl, or propyl group, R^2 is a methyl, ethyl or propyl group and T is an ethylene, propylene or butylene group.

In preferred embodiments, the linking group T is a lower aliphatic moeity (e.g., an alkylene, an alkenylene, or an alkynylene). The linking group may be substituted, e.g., with one or more amino, nitro, halogen, thiol or hydroxy groups.

A further aspect of the invention includes pharmaceutical compositions for treating amyloidosis. The therapeutic compounds in the methods of the invention, as described hereinbefore, can be incorporated into a pharmaceutical composition in an amount effective to modulate amyloidosis in a pharmaceutically acceptable vehicle.

The invention further contemplates the use of prodrugs which are converted *in vivo* to the therapeutic compounds of the invention (see, e.g., R.B. Silverman, 1992, "The Organic Chemistry of Drug Design and Drug Action", Academic Press, Chp. 8). Such prodrugs can be used to alter the biodistribution (e.g., to allow compounds which would not typically cross the blood-brain barrier to cross the blood-brain barrier) or the pharmacokinetics of the therapeutic compound. For example, an anionic group, e.g., a sulfate or sulfonate, can be esterified, e.g., with a methyl group or a phenyl group, to yield a sulfate or sulfonate ester. When the sulfate or sulfonate ester is administered to a subject, the ester is cleaved, enzymatically or non-enzymatically, reductively or hydrolytically, to reveal the anionic group. Such an ester can be cyclic, e.g., a cyclic sulfate or sultone, or two or more anionic moieties may be esterified through a linking group. In a preferred embodiment, the prodrug is a cyclic sulfate or sultone. An anionic group can be esterified with moieties (e.g., acyloxymethyl esters) which are cleaved to reveal an intermediate compound which subsequently decomposes to yield the active compound. In another embodiment, the prodrug is a reduced form of a sulfate or sulfonate, e.g., a thiol, which is oxidized *in vivo* to the therapeutic compound.

Furthermore, an anionic moiety can be esterified to a group which is actively transported *in vivo*, or which is selectively taken up by target organs. The ester can be selected to allow specific targeting of the therapeutic moieties to particular organs, as described in more detail below.

Within the therapeutic compound, the Y group(s) is covalently attached to a linking group T. Linking group T is advantageously of the formula $-(CD^1D^2)_n-$, wherein n is an integer from 1 to 25, C is carbon and D^1 and D^2 are independently hydrogen or halogen atoms; aliphatic, aromatic or heterocyclic groups; alkylamino or arylamino; or alkyloxy or aryloxy. As such, T may be a carbohydrate, polymer, peptide or peptide derivative, aliphatic group, alicyclic group, heterocyclic group, aromatic group or combinations thereof, and may further be substituted with, e.g., one or more amino, nitro, halogen, thiol or hydroxy groups. Suitable polymers include substituted and unsubstituted vinyl, acryl, styrene and carbohydrate-derived polymers and copolymers and salts thereof. Preferred linking T groups include a lower alkylene group, a heterocyclic group, a disaccharide, a polymer or a peptide or peptide derivative.

The linking T group may also include moieties which allow the therapeutic compound to be selectively delivered to a target organ or organs. For example, if delivery of a therapeutic compound to the brain is desired, a moiety capable of targeting the therapeutic compound to the brain, by either active or passive transport (a "targeting moiety") may be included. Illustratively, T may include a redox moiety, as described in, for example, U.S. Patents 4,540,564 and 5,389,623, both to Bodor. These patents disclose drugs linked to dihydropyridine moieties which can enter the brain, where they are oxidized to a charged pyridinium species which is trapped in the brain. Thus, drug accumulates in the brain. Other such moieties include compounds, such as amino acids or thyroxine, which can be passively or actively transported *in vivo*. Such a moiety can be metabolically removed *in vivo*, or can remain intact as part of an active compound. Structural mimics of amino acids (and other actively transported moieties) are also useful in the invention e.g., 1-(aminomethyl)-1-(sulfomethyl)-cyclohexane. Many targeting

moieties are known, and include, for example, asialoglycoproteins (see, e.g. Wu, U.S. Patent 5,166,320) and other ligands which are transported into cells via receptor-mediated endocytosis (see below for further examples of targeting moieties which may be covalently or non-covalently bound to a carrier molecule). Furthermore, the therapeutic compounds of the invention may bind to amyloidogenic proteins in the circulation and thus be transported to the site of action.

The targeting and prodrug strategies described above can be combined to produce a compound that can be transported as a prodrug to a desired site of action and then unmasked to reveal an active compound.

In methods of the invention, amyloid aggregation in a subject may be modulated by administering a therapeutic compound of the invention to a subject, i.e., *in vivo*. The term "subject" includes living organisms in which amyloidosis can occur. Examples of subjects include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. Administration of the compositions of the present invention to a subject to be treated can be carried out using known procedures, at dosages and for periods of time effective to modulate amyloid aggregation in the subject. An effective amount of the therapeutic compound necessary to achieve a therapeutic effect may vary according to factors such as the amount of amyloid already deposited at the clinical site in the subject, the age, sex, and weight of the subject, and the ability of the therapeutic compound to modulate amyloid aggregation in the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A non-limiting example of an effective dose range for a therapeutic compound of the invention (e.g., 3-acetylamino-1-propylsulfonic acid, sodium salt) is between 5 and 500 mg/kg of body weight/per day. In an aqueous composition, preferred concentrations for the active compound (i.e., the therapeutic compound that can modulate amyloid aggregation) are between 5 and 500 mM, more preferably between 10 and 100

mM, and still more preferably between 20 and 50 mM. For *N*-acetylated homotaurine derivatives, particularly preferred aqueous concentrations are between 10 and 20 mM.

The therapeutic compounds of the invention are effective when administered orally. Accordingly, a preferred route of administration is oral administration. Alternatively, the active compound may be administered by other suitable routes such as subcutaneous, intravenous, intraperitoneal, etc. administration (e.g., by injection). Depending on the route of administration, the active compound may be coated in a material to protect the compound from the action of acids and other natural conditions which may inactivate the compound.

The compounds of the invention can be formulated to ensure proper distribution *in vivo*. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds of the invention cross the BBB, they can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, e.g., U.S. Patents 4,522,811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs ("targeting moieties"), thus providing targeted drug delivery (see, e.g., V.V. Ranade (1989) *J. Clin. Pharmacol.* 29:685). Exemplary targeting moieties include folate or biotin (see, e.g., U.S. Patent 5,416,016 to Low *et al.*); mannosides (Umezawa *et al.*, (1988) *Biochem. Biophys. Res. Commun.* 153:1038); antibodies (P.G. Bloeman *et al.* (1995) *FEBS Lett.* 357:140; M. Owais *et al.* (1995) *Antimicrob. Agents Chemother.* 39:180); surfactant protein A receptor (Briscoe *et al.* (1995) *Am. J. Physiol.* 1233:134); gp120 (Schreier *et al.* (1994) *J. Biol. Chem.* 269:9090); see also K. Keinanen; M.L. Laukkanen (1994) *FEBS Lett.* 346:123; J.J. Killion; I.J. Fidler (1994) *Immunomethods* 4:273. In a preferred embodiment, the therapeutic compounds of the invention are formulated in liposomes; in a more preferred embodiment, the liposomes include a targeting moiety.

Delivery and *in vivo* distribution can also be affected by alteration of an anionic group of compounds of the invention. For example, anionic groups such

as carboxylate or tetrazole can be employed instead of, or in addition to, sulfate or sulfonate moieties, to provide compounds with desirable pharmacokinetic, pharmacodynamic, biodistributive, or other properties.

To administer the therapeutic compound by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the therapeutic compound may be administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan *et al.*, (1984) *J. Neuroimmunol.* 7:27).

The therapeutic compound may also be administered parenterally, intraperitoneally, intraspinally, or intracerebrally. Dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The vehicle can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like.

In many cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

Sterile injectable solutions can be prepared by incorporating the therapeutic compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the therapeutic compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient (i.e., the therapeutic compound) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The therapeutic compound can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The therapeutic compound and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the therapeutic compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the therapeutic compound in the compositions and preparations may, of course, be varied. The amount of the therapeutic compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in

association with the required pharmaceutical vehicle. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a therapeutic compound for the treatment of amyloid aggregation in subjects.

Active compounds are administered at a therapeutically effective dosage sufficient to modulate amyloid aggregation in a subject. A "therapeutically effective dosage" preferably modulates amyloid aggregation by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects. The ability of a compound to modulate amyloid aggregation can be evaluated in model systems that may be predictive of efficacy in modulating amyloid solubility and aggregation in human diseases, such as animal model systems known in the art or by *in vitro* methods including the thioflavine T assay, circular dichroism and electron microscopy. Other *in vitro* methods can be used to determine the ability of a compound to bind to the soluble amyloidogenic protein and keep it soluble, such as equilibrium dialysis, NMR and solubilization assays. Methods where adherence of soluble or non-soluble (e.g., fibrillary) amyloid protein to cell surface is monitored or determined include immunodetection of the protein at the cell surface, light microscopy, electron microscopy and flow cytometry.

The method of the invention is useful for treating amyloidosis associated with any disease in which amyloid aggregation occurs. Clinically, amyloidosis can be primary, secondary, familial or isolated. Amyloids have been categorized by the type of amyloidogenic protein contained within the amyloid. Non-limiting examples of amyloids which can be modulated, as identified by their amyloidogenic protein, are as follows (with the associated disease in parentheses after the amyloidogenic protein): ß-amyloid (Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage amyloidosis [Dutch]); amyloid A (reactive [secondary] amyloidosis, familial Mediterranean Fever, familial amyloid nephropathy with urticaria and deafness [Muckle-Wells syndrome]); amyloid κ L-

chain or amyloid λ L-chain (idiopathic [primary], myeloma or macroglobulinemia-associated); Ab2M (chronic hemodialysis); ATTR (familial amyloid polyneuropathy [Portuguese, Japanese, Swedish], familial amyloid cardiomyopathy [Danish], isolated cardiac amyloid, systemic senile amyloidosis); AIAPP or amylin (adult onset diabetes, insulinoma); atrial naturetic factor (isolated atrial amyloid); procalcitonin (medullary carcinoma of the thyroid); gelsolin (familial amyloidosis [Finnish]); cystatin C (hereditary cerebral hemorrhage with amyloidosis [Icelandic]); AApoA-I (familial amyloidotic polyneuropathy [Iowa]); AApoA-II (accelerated senescence in mice); fibrinogen-associated amyloid; lysozyme-associated amyloid; and AScr or PrP-27 (Scrapie, Creutzfeldt-Jacob disease, Gerstmann-Straussler-Scheinker syndrome, bovine spongiform encephalitis, and TSE).

The ability of a compound to modulate amyloid aggregation can be evaluated in an animal model system that may be predictive of efficacy in inhibiting amyloid aggregation in human diseases. The ability of a compound to inhibit amyloid aggregation can also be evaluated by examining the ability of the compound to inhibit amyloid aggregation *in vitro* or *ex vivo*, e.g., using an ELISA assay. The effect of a compound on the secondary structure of the amyloid can be further determined by circular dichroism (CD), infrared (IR) spectroscopy, and electron microscopy.

CD and IR spectroscopy are particularly useful techniques because the information obtained is a direct measure of the ability of a test compound to maintain the amyloid proteins in soluble non β-sheet form, by determining the structural effect of a compound on amyloid protein folding and/or fibril formation. This contrasts with previously known methods which measure cellular trafficking of amyloid protein precursors or interactions between amyloid and extracellular matrix proteins, providing only indirect evidence of potential amyloid-inhibiting activity. It should further be noted that CD and IR spectroscopy can also detect compounds which cause an increase in, e.g., β-sheet folding of amyloid protein, and thereby stabilize the formation of amyloid fibrils. Electron microscopy can be

used to visualize directly the ability of a compound to maintain the amyloid protein in a soluble non-fibrillar state.

The aggregation of amyloid is a multi-stage process. Accordingly, an agent useful for treating amyloidosis has many potential modes of action. An agent which inhibits amyloid aggregation, and the related cellular toxic effect , could act in one or more of the following ways, which are shown by way of illustration and not limitation:

1. Inhibition or delay of protein assembly or oligomerization in solution
2. Inhibition or delay of aggregation of amyloid assemblies or oligomers into insoluble β-sheet structures and/or aggregates
3. Disruption/dissolution/modification of insoluble amyloid fibrils and/or aggregates
4. Inhibition of the soluble or fibrillar amyloid protein binding to the cell surface, leading to a cellular activation process or toxicity.

Categories 1 and 2 correspond to prevention of the formation of amyloid aggregates (slowing down or halting amyloid aggregation), and category 3 corresponds to removal or modification of aggregates already formed (removal or reduction of existing amyloid aggregates). Category 4 focuses on the inhibition of the amyloid protein interaction in the cell surface.

The invention is further illustrated by the following examples which should not be construed as further limiting the subject invention. The contents of all references, issued patents, and published patent applications cited throughout this application are hereby incorporated by reference.

EXAMPLE 1

A solubility assay using Bradford detection was conducted to demonstrate the activity of certain therapeutic compounds in preventing or inhibiting Aβ fibril formation accordance with the present disclosure. Aβ peptides were synthesized using standard FMOC chemistry which was performed in conjunction with the

Biotechnology Centre, University of Toronto, and purified by HPLC. Alternatively, peptides can also be obtained from a number of commercial sources (e.g., BaChem and Peninsula Laboratories, California).

The assay was conducted as follows. Stock solution of Aß42 or Aß40 peptide at 5 mg/ml in distilled water, pH 7, and stock solutions of each test compound at 2 mg/ml in distilled water, pH 7 were prepared.

1. Mix 5µl (25µg) of stock Aß and 12.5 µl (25 µg) of stock test compounds into 1000 µl of 10 mM phosphate buffer, pH 7. This provides a molar ratio of roughly 1:10 [peptide:compound] assuming a general molecular weight of 400 daltons for the test compounds. Control samples were prepared for both peptide and compound. These contained Aß only using both 25 µg (5 µl stock Aß) and 50 µg (10µl stock Aß) to provide a standard curve for each run. Test compound controls contained 25 µg of material (12.5 µl of stock). All samples were mixed in 1000 µl of 10 mM phosphate buffer, pH 7 to final volume of 1017.5 µl.
2. Incubate all samples overnight at room temperature without mixing.
3. Spin at 14,000 rpm for 10 min in table top Eppendorf microfuge.
4. Take 800 µl of supernatant.
5. Add 200 µl of Bradford reagent (purchased from BioRad).
6. Mix well by vortexing.
7. Read at OD595 nm.

Compounds were characterized as "moderately active" if 25-50% of A•42 remained in the supernatant, "active" if 50-75% of Aß42 remained, and "very active" if >75% remained.

Active	Very active
XVII	XXII
	XXIX

EXAMPLE 2

An ELISA solubility assay was conducted to demonstrate the activity of certain therapeutic compounds in preventing or inhibiting Aβ fibril formation accordance with the present disclosure.

The assay was conducted as follows. Stock solution of Aβ42 peptide at 5 mg/ml in distilled water, pH 7, and stock solutions of each test compound at 1 mg/ml in distilled water, pH 7 were prepared.

1. A 10 μg sample of peptide was mixed with compound at a molar ratio of 1:10 [peptide:compound] in 500μl of 10 mM phosphate buffer. Control samples contained peptide only.
2. The mixture was incubated overnight at room temperature without agitation.
3. The incubated mixture was centrifuged at 14,000 rpm (Eppendorf microfuge) for 5 minutes to separate the soluble peptide.
4. 400 μl aliquots of supernatant were removed for ELISA assay.

ELISA

1. 100 μl of prepared samples were coated in 96 wells NUNC microplates (each sample tested in triplicate)
2. The plate was incubated at 37 °C for 3 hours, then at 4 °C overnight.
3. The wells were washed twice with 0.05% Tween 20 in phosphate buffered saline.
4. 250 μl of 3% skim milk powder in PBS was used to block non-specific binding to the wells (at 37 °C for 1.5 hours)

5. The wells were washed with 0.05% Tween 20 / PBS twice.

6. A 100 µl aliquot of diluted (final dilution 1:100 in PBS) mouse monoclonal anti-Aβ antibody (purchased from DAKO recognizing the N-terminal residues 1-10) was added to each well. The antibody was then incubated at 37 C for 2 Hours.

7. The wells were washed with 0.05% Tween 20/ PBS six times (5 min/wash).

8. Visualization was performed using 100 µl of diluted goat anti-mouse IgG (H+L) conjugated with alkaline phosphatase (purchased from BioRad) was added to each well. The plate was incubated at 37 °C for 1 hour.

9. The wells were washed with 0.05% Tween 20 / PBS six times (5 min/wash).

10. The color reaction was developed using 100 µl of alkaline phosphatase substrate (purchased from BioRad) which was added to each well.

11. The relative amounts of Aβ were obtained by measuring the OD of the sample at 405 nm using a standard ELISA plate reader.

Compounds were characterized as "active" if 40-50% of Aß42 remained in the supernatant.

Active
XXIV
XXVIII
XXI

EXAMPLE 3

Circular dichroism analysis was conducted to demonstrate the activity of certain therapeutic compounds in preventing or inhibiting Aβ40 fibril formation accordance with the present disclosure by determining the presence or absence of β-sheet conformation.

The assay is conducted as follows:

INSTRUMENT AND PARAMETERS

Instrument: JASCO J-715 Spectropolarimeter.
Cell/cuvette: Hellma quartz (QS) with 1.0 mm pathlength
Room temperature.
Wavelength interval: 250 nm-190 nm.
Resolution: 0.1 nm.
Band width: 1.0 nm
Response time: 1 sec
Scanning speed: 20 nm/min
Number of accumulations/spectrum: 5

PRE-INCUBATION ASSAY

1. Prepare a fresh 40μm solution of Aβ(1-40) in 0.02M Tris, pH 7.4.
2. Prepare a 1mM solution of test compounds in 0.02M Tris, pH 7.4.
3. Combine equal volumes of the Aβ(1-40) and test compound solutions.
4. Incubate the mixtures for 19h.
5. Take the CD spectrum using the parameters above.
6. Return the mixtures to the incubator and incubate to 43h.
7. Take the CD spectrum using the parameters above.

Inhibition of Aβ40 assembly/aggregation is determined by comparing the amount of b-sheet structure)appearing at lambda=218nm) obtained in control and in treated sample at each timepoint.

Compound	Incubation time		
	0h	19h	43h
XVII	-[1,2]	+	++
III	-	+	++
VII	+	++	++
IX	+	+++	++
VIII	+	++++	+++
X	+	++	++
XXII	+	++++	++
LVXIII	-	++++	-
LVXV	+	++++	++
LVXVI	+	+++	++
XXXVIII	-	+++	++

[1]No effect compared to Aβ alone

[2]Key: relative inhibition compared to Aβ alone : +: 0-25%; ++: 25-50%; +++: 50-75%; ++++: 75-100%

EXAMPLE 4

CD analysis was conducted as above to demonstrate the activity of certain therapeutic compounds in preventing or inhibiting IAPP fibril formation.

Compound	Activity
XLIII	-
XXXVIII	Active
XLII	Active

EXAMPLE 5

Secondary amyloidosis *in vivo* results.

The *in vivo* screening is based on the acute AEF-$AgNO_3$-induced amyloidosis mouse model. The test is conducted on a total of 6 days and each compound administered in the drinking solution for a 5-day period.

Female mice of CBA/J strain are individually identified, weighed and assigned to a group of 5 animals following an acclimation period. The amyloidosis is induced by intravenous injection of 100 µg of AEF (amyloid enhancing factor) concomitantly with a subcutaneous injection of 0.5 ml of 2% of a solution of $AgNO_3$. Animals in the negative control group are injected with saline only.

Twenty-four hours following the amyloidosis induction, the compound is added to a 1% solution of sucrose (vehicle) and distributed to animals in drinking bottles for a period of 5 days. Animals in the positive control group receive the vehicle only. Drinking solutions are made available *ad libitum* to each group of animals and the volume measured before and after use to calculate the consumption of each solution. Blood samples are collected for *in vitro* determination of plasma serum amyloid A levels.

On day 6, mice are sacrificed, weighed and organs such as spleen are existed and fixed in acid alcohol. Spleen samples are processed, embedded in paraffin wax and cut inyo sections. Spleen sections from each animal are stained with the Congo Red staining solution and the splenic Amyloid A fibrils aggregation evaluated by image analysis. Results are expressed as % of AA fibrils deposited in the splenic perifollicular area. Raw data is analyzed.

Mean of mouse body weight and the mean consumption of the drinking solution (ml) are compiled. Variation of the body weight before the induction and at the end of the assay is calculated (%). The dose level of the compound consumed (mg/kg/day) is calculated as well.

P-values for Student t-test and Mann-Whitney tests comparing a group to the positive control are calculated using GraphPad Prism computer software.

The mean of the image analysis reading of spleen serious for a group is expressed as percentage of the mean of the image analysis readings for the positive control group (%PC).

Compound	Concentration (mg/ml)	%PC	Activity
I	6.25 12.5 25.0	87 76%, 68% 69%	Moderate
III	3.5 6.25 12.5 25.0	113% 87% 54%, 67%, 56% 82%, 77%	Moderate
VII	6.25 12.5 25.0	94%, 91% 83% 71%, 97%	Moderate
IX	6.25 12.5	74%, 40% 64%, 38%	Active
XVIII	3.13 6.25	74% 86%	Moderate
XX	6.25 12.5	94% 69%	Moderate

The effectiveness of compounds of the invention, **XXVII** and **XVII** are shown in Figures 11 and 12, which are histograms showing results using the above animal model.

EXAMPLE 6

Determination of the rate of amyloid fibril formation by Thioflavine T spectroscopy

Thioflavine T (ThT) binds to amyloid proteins in β-sheet formation, exhibiting a yellow fluorescence from tissue sections and fibrils *in vitro*. Detection of ThT fluorescence can be used as a sensitive assay for amyloid fibril formation under different conditions. This assay has been used in experiments to determine the effects of compounds of the invention on amyloid fibril formation.

Method

Human IAPP was dissolved in 40% trifluoroethanol and freeze-dried into conveniently-sized aliquots. IAPP was prepared immediately before the measurements by dissolving in 40% 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) in water to maintain the peptide in alpha helical conformation and soluble. A stock solution of ThT (2.5mM) was prepared, 7.9mg in 10mL Tris-HCl pH 7.0 and filtered (0.22 μm). Solutions were kept in the dark until use. Fluorescence was examined at 440nm excitation (slit 5nm), and emission at 482nm (slit 10nm) with stirring. 25ml of ThT stock (final concentration 62.5 μM) was added to peptide sample and made up to 1mL in the cuvette. The sample was stirred for 5 min. before taking a reading. Measurements were made at an initial time point (5 min. from sample preparation), at intervals over the next 4-6h and after overnight incubation at room temperature.

Certain compounds as disclosed herein, i.e., 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; DL-2-amino-5-phosphovaleric acid; 4-Phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine; cyclohexylsulfamic acid; *O*-phospho-*L*-serine; 8-methoxyquinoline-5-sulfonic acid; 3-amino-2-hydroxy-1-propanesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid, and 1,2,3,4-tetrahydroisoquinoline, were found to inhibit or prevent IAPP-associated fibril assembly.

EXAMPLE 7

Circular dichroism analysis was conducted to confirm the activity of certain therapeutic compounds in preventing or inhibiting IAPP-associated fibril formation in accordance with the present disclosure by determining the presence or absence of β-sheet conformation.

The assay is conducted as follows:

INSTRUMENT AND PARAMETERS

Instrument: JASCO J-715 Spectropolarimeter
Cell/cuvette: Hellma quartz (QS) with 1.0 mm pathlength
Room temperature
Wavelength interval: 250 nm-190 nm
Resolution: 0.1 nm
Band width: 1.0 nm
Response time: 1 sec
Scanning speed: 20 nm/min
Number of spectra run: 5

The assay, a co-incubation procedure, examines the ability of a compound or substance to inhibit the assembly of amyloid fibrils, e.g., to test for the presence of the amyloidotic β-sheet conformation in the presence of soluble IAPP. Samples are run in the presence and absence (i.e., water alone) of buffering agent, which is done to determine if competitive effects are seen with the ionic buffer (usually phosphate).

A. Assay in Water Only

Add components used at a molar ratio of 1:10 [peptide:compound]; add 10 μL of 10 mg/mL IAPP stock solution (final 100 μg peptide) to the aqueous solution containing compound to a final volume of 400 μl. The pH of the final assay solution is measured to ensure there is no fluctuation and the spectrum is accumulated using the parameters as shown above.

B. Assay in Phosphate Buffer

Add desired amount of compound to achieve a 1:10 molar ratio in 10 mM phosphate buffer, pH 7. Add 10 μL of 10 mg/mL IAPP stock solution (final peptide 100 μg) to the phosphate buffered solution containing the compound and bring to a final volume of 400 μL. The pH of the final assay solution is measured to ensure there is no fluctuation and the spectrum is accumulated using the parameters as shown above.

In both assays, a control sample is run with each test group. This control contains peptide only in water or buffer at a similar final volume of 400 μl. Spectra for the control are collected initially (first run) and at the end of the test

(final run) to ensure that the peptide has not undergone extensive aggregation during the course of the assay. Spectra for the controls are used to compare with the measurements obtained with the treated samples.

CO-INCUBATION:

Make fresh 1 mg/mL stock solution of IAPP in 10 mM phosphate buffer, pH 7. Add desired amount of compound to achieve a 1:10 molar ratio in 10 mM phosphate buffer, pH 7. Incubate for 3 days at room temperature. Make up to final volume of 400 μL with 10 mM phosphate buffer, pH 7. The pH of the final assay solution is measured to ensure there is no fluctuation and the spectrum is accumulated using the parameters as shown above.

A similar control is run for comparative purposes.

DATA ANALYSIS

Plots of the spectra (control and treated) are individually assembled and the changes in ellipticity at 218 nm are examined. This minimum is directly correlated with the amount of β-sheet present in the sample. Changes in either a positive or negative direction are noted and a relative value ("active" or "not active") assigned to the compound as a measure of activity. In a subsequent experiment with the compounds at a molar ratio of 1:5 [peptide:compound], the degree of randomness was noted, an indication of the ability of the compounds to prevent amyloid aggregation. A more positive number indicates less β-sheet formation. The ability of a compound to prevent β-sheet formation for at least 24h is important, as the non-aggregated amyloid fibrils will be excreted in the soluble form. In the control noted below, the decrease in CD (mdegs) may indicate that some of the peptide is aggregating under these conditions.

Compound	Activity	T_0	24h	48h
Control IAPP	-	Random	β (-2)	β (-1.5)
3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid **(LVX)**	Active	Random	Random	β (-1.7)
DL-2-amino-5-phosphovaleric acid **(LVIII)**	Active	Random	Random	β (-3.5)
1,2,3,4-tetrahydroisoquinoline**(LVIX)**	Active	Random	β (-1.5)	β (-1.3)
cyclohexylsulfamic acid**(LVXI)**	Active	Random	β (-1.1)	β (-0.8)
O-phospho-L-serine **(LVXII)**	Active	Random	Random	β (-2.0)
8-methoxyquinoline-5-sulfonic acid**(LVXIV)**	Active	Random	β (-1.3)	β (-0.8)
4-Phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine, sodium salt **(LVXV)**	Active	Random	Random	β (-1.8)
3-amino-2-hydroxy-1-propanesulfonic acid **(LVXVI)**	Active	-	-	-
3-dimethylamino-1-propanesulfonic acid **(LVXVII)**	Active	Random	β (-1.7)	β (-1.5)

EXAMPLE 8

The synthesis of a compound of the invention, 4-Phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine, is described below.

To a solution of 4-phenylpyridine (15.5 g, 0.1 mol) in acetone (100 mL) was added 1,3-propane sultone (12.2 g, 0.1 mol) at room temperature. The mixture was then heated at reflux temperature overnight. The resultant suspension was cooled to room temperature. The solid was collected by filtration and washed with acetone. To a solution of the solid (31 g) in methanol (500 mL) was added sodium borohydride (10 g, 260 mmol) portionwise, and the mixture was stirred at room temperature for 2 h. Distilled water (50 mL) was added to destroy the excess of sodium borohydride. The mixture was diluted with methanol (200 ml), and neutralized with Amberlite IR-120 ion-exchange resin (H^+ form, 300 g). A white

precipitate was formed. The precipitate and the resin were removed by filtration and treated with distilled water (400 mL) at ~100 °C. The mixture was filtered and the residual resin was washed with hot distilled water (2 x 200 mL). The filtrates and washings were combined and concentrated to dryness. The residue was co-evaporated with methanol (3 x 200 mL), and then recrystallized from ethanol–water {8:2 (v/v)} to afford 4-phenyl-1-(3′-sulfopropyl)-1,2,3,6-tetrahydropyridine as white crystals (26 g, 93%). The ^{1}H and ^{13}C NMR spectra were in agreement with the structure.

To a solution of 4-phenyl-1-(3′-sulfopropyl)-1,2,3,6-tetrahydropyridine (5.6 g, 20 mmol) obtained above in ethanol (180 mL) was added sodium hydroxide (1.2 g, 30 mmol). The suspension was heated at reflux temperature for 30 min. The mixture was then cooled to room temperature. The first crop of product (3.9 g, 64%) was collected by filtration. The filtrate was concentrated to dryness, and the residue was recrystallized from ethanol to afford the second crop of product (2.0 g, 32%). ^{1}H NMR (400 MHz, D_2O): δ 1.85 (quintet, 2 H, J 8.7, 7.7 Hz, 2 H-2′), 2.39–2.45 (m, 4 H, 2 H-3′ and 2 H-3), 2.59 (t, 2 H, J 5.6 Hz, 2 H-2), 2.80 (t, 2 H, J 7.7 Hz, 2 H-1′), 3.00 (br s, 2 H, 2 H-6), 6.00 (br s, 1H, H-5), 7.18–7.36 (m, 5 H, Ar). ^{13}C NMR (100.6 MHz, D_2O): δ 23.90 (C-2′), 29.01 (C-3), 51.69, 51.76 (C-2, C-3′), 54.45 (C-6), 58.12 (C-1′), 123.75 (C-5), 127.31, 130.01, 131.24 (Ar), 136.89 (C-4), 142.47 (Ar).

EXAMPLE 9

The synthesis of a compound of the invention, 8-methoxy-5-quinolinesulfonic acid, sodium salt, is described below.

8-methoxy-5-quinoline (3.8 g. sublimated) was added to cold chlorosulfonic acid (30 mL at 2°C) over 30 min. The reaction mixture was stirred at room temperature (ca. 20°C) for 1h. TLC showed complete consumption of starting material at this time. The reaction mixture was poured onto ice (200 g), and sodium carbonate (70 g) was then added. The solid material was collected by filtration and then dissolved in ethyl acetate (250 mL) which was then washed with

water. The organic layer was then separated and (Na_2CO_3). The organic layer was then filtered and the solvent was evaporated *in vacuo* to yield 8-methoxy-5-quinolinesulfonyl chloride as a white solid (2.9g).

8-Methoxy-5-quinolinesulfonyl chloride (773 mg, see above) was treated with a solution of sodium hydroxide (120 mg) in water at 50°C for 12h. The resulting sodium salt (700 mg) was recrystallized from H_2O to give the title compound as a yellow powder (300 mg). The NMR spectrum of 8-Methoxy-5-quinolinesulfonyl chloride, sodium salt (in deuterated DMSO) is shown in Figure 10.

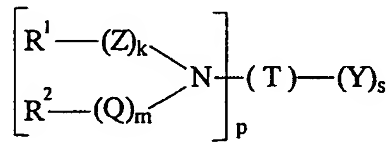
EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims. The contents of all references, issued patents, and published patent applications cited throughout this application are hereby incorporated by reference.

CLAIMS

What is claimed is:

1. A method for modulating amyloid aggregation in a subject, comprising administering to a subject an effective amount of a therapeutic compound such that modulation of amyloid aggregation occurs, wherein the therapeutic compound has the formula:



wherein

- R^1 and R^2 are each independently a hydrogen atom or a substituted or unsubstituted aliphatic or aryl group;

- Z and Q are each independently a carbonyl (C=O), thiocarbonyl (C=S), sulfonyl (SO_2), or sulfoxide (S=O);

- k and m are 0 or 1, provided when k is 1, R^1 is not a hydrogen atom and when m is 1, R^2 is not a hydrogen atom;

- p and s are each independently positive integers selected such that the biodistribution of the therapeutic compound for an intended target site is not prevented while maintaining activity of the therapeutic compound;

- T is a linking group; and

- Y is a group of the formula -AX wherein A is an anionic group at physiological pH, and X is a cationic group.

2. The method of claim 1 wherein at least one of k or m equals 1.

3. The method of claim 1, wherein said therapeutic compound prevents or inhibits said amyloid aggregation.

4. The method of claim 1, wherein R^1 is an alkyl or alkenyl, or aryl group, k is one, Z is a carbonyl group, R^2 is a hydrogen atom or an alkyl group, m is zero, p and s are 1, T is an alkylene group, and A is SO_3^-.

5. The method of claim 4, wherein said therapeutic compound is selected from the group consisting of 3-acetylaminopropanesulfonic acid, 3-benzoylamino-1-propanesulfonic acid sodium salt, and 2-acrylamido-2-methyl-1-propanesulfonic acid.

6. The method of claim 1, wherein R^1 and R^2 are alkyl, alkenyl, or aryl groups, or R^1 and R^2 are taken together to form an alkylene group, k and m are each one, Z and Q are each independently a carbonyl or a sulfonyl groups, p and s are 1, T is an alkylene group, and A is SO_3^-.

7. The method of claim 6, wherein said therapeutic compound is selected from the group consisting of 3-phthalimido-1-propanesulfonic acid, N-(3-sulfopropyl)saccharin and 4-phthalimido-1-butanesulfonic acid.

8. The method of claim 1, wherein R^1 is a hydrogen, an alkyl, an alkenyl, or an aryl group, k and m are zero, R^2 is a hydrogen atom or an alkyl group, p and s are each one, T is an alkylene group, and A is SO_3^-.

9. The method of claim 8, wherein said therapeutic compound is selected from the group consisting of 3-phenylamino-1-propanesulfonic acid sodium salt, 3-(4-pyridylamino)]-1-propanesulfonic acid, 3-(benzylamino)-1-propanesulfonic acid, diethylphosphonoacetic acid, phosphonoformic acid, trisodium salt, 3-benzoylaminopropanesulfonic acid, 2-deoxy-2-(3-sulfopropyl)amino-D-glucose, 1-phenyl-2,3,-dimethyl-4-methylamino-pyrazolon-5-*N*-methylsulfonic acid, 3-[(-3,4-dimethyl-1-adamantyl)-amino]-1-propanesulfonic acid, 3-(2-hydroxyethyl)amino-1-propanesulfonic acid, 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid, (-)-3-[(*R*)-2-hydroxy-1-propyl]amino-1-propanesulfonic acid, 3-[(*d,l*)-2-hydroxy-1-propyl]-1-propanesulfonic acid, 3-(4-hydroxy-1-butyl)amino-1-propanesulfonic acid, 3-(5-hydrox-1-pentyl)amino-1-propanesulfonic acid, 3-(6-hydroxy-1-hexyl)amino-1-propanesulfonic acid, 3-(4-hydroxyphenyl)amino-1-propanesulfonic acid, (+)-3-[(*S*)-2-hydroxy-1-propyl]amino-1-propanesulfonic acid, (+)-3-[(*S*)-1-hydroxy-2-propyl]amino-1-propanesulfonic acid, (-)-3-[(*R*)-1-hydroxy-2-propyl]amino-1-propanesulfonic acid, (+)-3-[(*S*)-1-hydroxy-2-butyl]amino-1-propanesulfonic acid, (-)-3-[(*R*)-1-

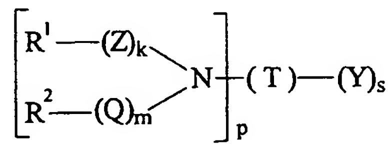
hydroxy-2-butyl]amino-1-propanesulfonic acid, 3-[(*dl*)-5-hydroxy-2-pentyl]amino-1-propanesulfonic acid, 3-[(*dl*)-6-hydroxy-2-hexyl]amino-1-propanesulfonic acid, 3-amylamino-1-propanesulfonic acid, 3-hexylamino-1-propanesulfonic acid, 3-heptylamino-1-propanesulfonic acid, 3-octylamino-1-propanesulfonic acid, 3-nonylamino-1-propanesulfonic acid, 3-decylamino-1-propanesulfonic acid, 3-undecylamino-1-propanesulfonic acid, 3-dodecylamino-1-propanesulfonic acid, 3-tridecylamino-1-propanesulfonic acid, 3-tetradecylamino-1-propanesulfonic acid, 3-hexadecylamino-1-propanesulfonic acid, 3-octadecylamino-1-propanesulfonic acid, dimethyl(3-sulfopropyl)-tetradecylammonium hydroxide, inner salt,), and 2-(3-Sulfobutyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-b] indole, sodium salt.

10. The method of claim 1 wherein R^1 and R^2 are each independently an alkyl, alkenyl, or an aryl group, or R^1 and R^2 are taken together to form an alkylene group, k and m are zero, p and s are each one, T is an alkylene group, and A is SO_3^-.

11. The method of claim 10, wherein said therapeutic compound is selected from the group consisting of 3-dimethylamino-1-propanesulfonic acid, 4-(1-piperidinyl)-1-butanesulfonic acid, 3-[1-(1,2,3,6-tetrahydropyridyl)]-1-propanesulfonic acid, 3-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-[2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-[1-(1,2,3,4-tetrahydroquinolinyl)]-1-propanesulfonic acid, 2-(3-sulfopropyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole, sodium salt, 3-(1-indolinyl)-1-propanesulfonic acid, 3-[2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-(2-isoindolinyl)-1-propanesulfonic acid, 3-(4-benzyl-1-piperidinyl)-1-propanesulfonic acid, 1-(3-sulfopropyl)-(*S*)-nicotinium hydroxide inner salt, 3-[2-(1,2,3,4,5,6,7,8-octahydroisoquinolinyl)]-1-propanesulfonic acid, Thiazol Yellow G, 3-sulfolmethylphenylalanine, Chicago Sky Blue 6B, 4-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-1-butanesulfonic acid, and 3-Sulfomethyl-L-phenylalanine.

12. A method for treating a disease state associated with amyloidosis, comprising:

- administering to a subject an effective amount of a therapeutic compound such that a disease state associated with amyloidosis is treated, wherein the therapeutic compound has the formula



wherein

- R^1 and R^2 are each independently a hydrogen atom or a substituted or unsubstituted aliphatic or aryl group;
- Z and Q are each independently a carbonyl (C=O), thiocarbonyl (C=S), sulfonyl (SO_2), or sulfoxide (S=O);
- k and m are 0 or 1, provided when k is 1, R^1 is not a hydrogen atom and when m is 1, R^2 is not a hydrogen atom;
- p and s are each independently positive integers selected such that the biodistribution of the therapeutic compound for an intended target site is not prevented while maintaining activity of the therapeutic compound;
- T is a linking group; and
- Y is a group of the formula -A X wherein A is an anionic group at physiological pH, and X is a cationic group.

13. The method of claim 12 wherein at least one of k or m equals 1.

14. The method of claim 12, wherein said disease state is amyloid aggregation associated with Alzheimer's Disease.

15. The method of claim 12, wherein R^1 is an alkyl, an alkenyl, or an aryl group, k is one, Z is a carbonyl group, R^2 is a hydrogen atom or an alkyl group, m is zero, p and s are 1, T is an alkylene group, and A is SO_3^-.

16. The method of claim 14, wherein said therapeutic compound is selected from the group consisting of 3-acetylaminopropanesulfonic acid, 3-benzoylamino-1-propanesulfonic acid, and 2-acrylamido-2-methyl-1-propanesulfonic acid.

17. The method of claim 12, wherein R^1 and R^2 are each independently an alkyl, an alkenyl, or an aryl group, or R^1 and R^2 are taken together to form an alkylene group, k and m are each one, Z and Q are each independently a carbonyl or a sulfonyl group, p and s are 1, T is an alkylene group, and A is SO_3^-.

18. The method of claim 16, wherein said therapeutic compound is selected from the group consisting of 3-phthalimido-1-propanesulfonic acid, N-(3-sulfopropyl)saccharin, and 4-phthalimido-1-butanesulfonic acid.

19. The method of claim 12, wherein said therapeutic compound is administered orally.

20. The method of claim 12, further comprising administering the therapeutic compound in a pharmaceutically acceptable vehicle.

21. The method of claim 12, wherein R^1 is a hydrogen, an alkyl, an alkenyl, or an aryl group, k and m are zero, R^2 is hydrogen or an alkyl group, p and s are each one, T is an alkylene group, and A is SO_3^-.

22. The method of claim 20, wherein said therapeutic compound is selected from the group consisting of 3-phenylamino-1-propanesulfonic acid sodium salt, 3-(4-pyridinylamino)]-1-propanesulfonic acid, 3-(benzylamino)-1-propanesulfonic acid, diethylphosphonoacetic acid, phosphonoformic acid, trisodium salt, 3-benzoylaminopropanesulfonic acid, 2-deoxy-2-(3-sulfopropyl)amino-D-glucose, 1-phenyl-2,3,-dimethyl-4-methylamino-pyrazolon-5-*N*-methylsulfonic acid, 3-[(-3,4-dimethyl-1-adamantyl)-amino]-1-propanesulfonic acid, 3-(2-hydroxyethyl)amino-1-propanesulfonic acid, 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid, (-)-3-[(*R*)-2-hydroxy-1-propyl]amino-1-propanesulfonic acid, 3-[(*d,l*)-2-hydroxy-1-propyl]-1-propanesulfonic acid, 3-(4-hydroxy-1-butyl)amino-1-propanesulfonic acid, 3-(5-hydrox-1-pentyl)amino-1-propanesulfonic acid, 3-(6-hydroxy-1-hexyl)amino-1-propanesulfonic acid, 3-(4-hydroxyphenyl)amino-1-propanesulfonic acid, (+)-3-[(*S*)-2-hydroxy-1-propyl]amino-1-propanesulfonic acid, (+)-3-[(*S*)-1-hydroxy-2-propyl]amino-1-propanesulfonic acid, (-)-3-[(*R*)-

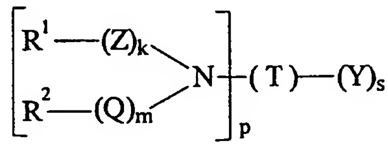
1-hydroxy-2-propyl]amino-1-propanesulfonic acid, (+)-3-[(*S*)-1-hydroxy-2-butyl]amino-1-propanesulfonic acid, (-)-3-[(*R*)-1-hydroxy-2-butyl]amino-1-propanesulfonic acid, 3-[(*dl*)-5-Hydroxy-2-pentyl]amino-1-propanesulfonic acid, 3-[(*dl*)-6-hydroxy-2-hexyl]amino-1-propanesulfonic acid, 3-amylamino-1-propanesulfonic acid, 3-hexylamino-1-propanesulfonic acid, 3-heptylamino-1-propanesulfonic acid, 3-octylamino-1-propanesulfonic acid, 3-nonylamino-1-propanesulfonic acid, 3-decylamino-1-propanesulfonic acid, 3-undecylamino-1-propanesulfonic acid, 3-dodecylamino-1-propanesulfonic acid, 3-tridecylamino-1-propanesulfonic acid, 3-tetradecylamino-1-propanesulfonic acid, 3-hexadecylamino-1-propanesulfonic acid, 3-octadecylamino-1-propanesulfonic acid, dimethyl(3-sulfopropyl)-tetradecylammonium hydroxide, inner salt, and 2-(3-Sulfobutyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-b] indole, sodium salt.

23. The method of claim 12, wherein R^1 and R^2 are alkyl, alkenyl, or aryl groups, or R^1 and R^2 are taken together to form an alkylene group, k and m are zero, p and s are each one, T is an alkylene group, and A is SO_3^-.

24. The method of claim 22, wherein said therapeutic compound is selected from the group consisting of 3-dimethylamino-1-propanesulfonic acid, 4-(1-piperidinyl)-1-ethanesulfonic acid, 3-[1-(1,2,3,6-tetrahydropyridyl)]-1-propanesulfonic acid, 3-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-[2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-[1-(1,2,3,4-tetrahydroquinolinyl)]-1-propanesulfonic acid, 2-(3-sulfopropyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole, sodium salt, 3-(1-indolinyl)-1-propanesulfonic acid, 1-(3-sulfopropyl)-(*S*)-nicotinium hydroxide inner salt, 3-[2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-(2-isoindolinyl)-1-propanesulfonic acid, 3-(4-benzyl-1-piperidinyl)-1-propanesulfonic acid, 3-[2-(1,2,3,4,5,6,7,8-octahydroisoquinolinyl)]-1-propanesulfonic acid, Thiazol Yellow G, 3-sulfonylmethylphenylalanine, Chicago Sky Blue 6B, 4-[2-(1,2,3,4-

tetrahydroisoquinolinyl)]-1-butanesulfonic acid, and 3-Sulfomethyl-L-phenylalanine.

25. A composition for modulating amyloidosis, comprising a compound having the formula:



wherein

- R^1 and R^2 are each independently a hydrogen atom or a substituted or unsubstituted aliphatic or aryl group;
- Z and Q are each independently a carbonyl (C=O), thiocarbonyl (C=S), sulfonyl (SO_2), or sulfoxide (S=O);
- k and m are 0 or 1, provided when k is 1, R^1 is not a hydrogen atom and when m is 1, R^2 is not a hydrogen atom;
- p and s are each independently positive integers selected such that the biodistribution of the therapeutic compound for an intended target site is not prevented while maintaining activity of the therapeutic compound;
- T is a linking group; and
- Y is a group of the formula -A X wherein A is an anionic group at physiological pH, and X is a cationic group, in an amount sufficient to inhibit amyloid aggregation in a subject.

26. The composition of claim 25, wherein at least one of k or m equals 1.

27. The composition of claim 24, wherein said disease state is amyloid aggregation associated with Alzheimer's Disease.

28. The composition of claim 25, wherein R^1 is an alkyl, alkenyl, or aryl group, k is one, Z is a carbonyl group, R^2 is a hydrogen atom or an alkyl group, m is zero, p and s are 1, T is an alkylene group, and A is SO_3^-.

29. The composition of claim 28, wherein said compound is selected from the group consisting of 3-acetylaminopropanesulfonic acid, 3-benzoylamino-1-propanesulfonic acid, and 2-acrylamido-2-methyl-1-propanesulfonic acid.

30. The composition of claim 25, wherein R^1 and R^2 are each independently an alkyl, alkenyl, or aryl group, or R^1 and R^2 are taken together to form an alkylene group, k and m are each one, Z and Q are each independently a carbonyl or a sulfonyl group, p and s are 1, T is an alkylene group, and A is SO_3^-.

31. The composition of claim 30, wherein said compound is selected from the group consisting of 3-phthalimido-1-propanesulfonic acid, N-(3-sulfopropyl) saccharin, and 4-phthalimido-1-butanesulfonic acid.

32. The composition of claim 25, wherein R^1 is a hydrogen, an alkyl, an alkenyl, or an aryl group, k and m are zero, R^2 is hydrogen or an alkyl group, p and s are each one, T is an alkylene group, and A is SO_3^-.

33. The composition of claim 32, wherein said compound is selected from the group consisting of 3-phenylamino-1-propanesulfonic acid sodium salt, 3-(4-pyridylamino)]-1-propanesulfonic acid, 3-(benzylamino)-1-propanesulfonic acid, diethylphosphonoacetic acid, phosphonoformic acid, trisodium salt, 3-benzoylaminopropanesulfonic acid, 2-deoxy-2-(3-sulfopropyl)amino-D-glucose, 1-phenyl-2,3,-dimethyl-4-methylamino-pyrazolon-5-*N*-methylsulfonic acid, 3-[(-3,4-dimethyl-1-adamantyl)-amino]-1-propanesulfonic acid, 3-(2-hydroxyethyl)amino-1-propanesulfonic acid, 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid, (-)-3-[(*R*)-2-hydroxy-1-propyl]amino-1-propanesulfonic acid, 3-[(*d,l*)-2-hydroxy-1-propyl]-1-propanesulfonic acid, 3-(4-hydroxy-1-butyl)amino-1-propanesulfonic acid, 3-(5-hydrox-1-pentyl)amino-1-propanesulfonic acid, 3-(6-hydroxy-1-hexyl)amino-1-propanesulfonic acid, 3-(4-hydroxyphenyl)amino-1-propanesulfonic acid, (+)-3-[(*S*)-2-hydroxy-1-propyl]amino-1-propanesulfonic acid, (+)-3-[(*S*)-1-hydroxy-2-propyl]amino-1-propanesulfonic acid, (-)-3-[(*R*)-1-hydroxy-2-propyl]amino-1-propanesulfonic acid, (+)-3-[(*S*)-1-hydroxy-2-butyl]amino-1-propanesulfonic acid, (-)-3-[(*R*)-1-

hydroxy-2-butyl]amino-1-propanesulfonic acid, 3-[(*dl*)-5-Hydroxy-2-pentyl]amino-1-propanesulfonic acid, 3-[(*dl*)-6-hydroxy-2-hexyl]amino-1-propanesulfonic acid, 3-amylamino-1-propanesulfonic acid, 3-hexylamino-1-propanesulfonic acid, 3-heptylamino-1-propanesulfonic acid, 3-octylamino-1-propanesulfonic acid, 3-nonylamino-1-propanesulfonic acid, 3-decylamino-1-propanesulfonic acid, 3-undecylamino-1-propanesulfonic acid, 3-dodecylamino-1-propanesulfonic acid, 3-tridecylamino-1-propanesulfonic acid, 3-tetradecylamino-1-propanesulfonic acid, 3-hexadecylamino-1-propanesulfonic acid, 3-octadecylamino-1-propanesulfonic acid, dimethyl(3-sulfopropyl)-tetradecylammonium hydroxide, inner salt, and 2-(3-Sulfobutyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-b] indole, sodium salt.

34. The composition of claim 25, wherein R^1 and R^2 are each independently an alkyl, alkenyl, or aryl group, or $R^1$and R^2 are taken together to form an alkylene group, k and m are zero, p and s are each one, T is an alkylene group, and A is SO_3^-.

35. The composition of claim 35, wherein said compound is selected from the group consisting of 3-dimethylamino-1-propanesulfonic acid, 4-(1-piperidinyl)-1-ethanesulfonic acid, 3-[1-(1,2,3,6-tetrahydropyridyl)]-1-propanesulfonic acid, 3-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-[2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-[1-(1,2,3,4-tetrahydroquinolinyl)]-1-propanesulfonic acid, 2-(3-sulfopropyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole, sodium salt, 3-(1-indolinyl)-1-propanesulfonic acid, 1-(3-sulfopropyl)-(*S*)-nicotinium hydroxide inner salt, 3-[2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-(2-isoindolinyl)-1-propanesulfonic acid, 3-(4-benzyl-1-piperidinyl)-1-propanesulfonic acid, 3-[2-(1,2,3,4,5,6,7,8-octahydroisoquinolinyl)]-1-propanesulfonic acid, Thiazol Yellow G, 3-sulfonylmethylphenylalanine, Chicago Sky Blue 6B, 4-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-1-butanesulfonic acid, and 3-Sulfomethyl-L-phenylalanine.

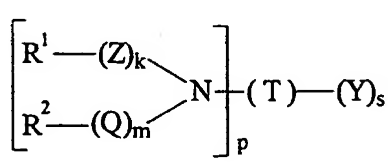
36. The composition of claim 25, wherein said compound is selected from the group consisting of 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; DL-2-amino-5-phosphovaleric acid; 4-Phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine; cyclohexylsulfamic acid; *O*-phospho-*L*-serine; 8-methoxyquinoline-5-sulfonic acid; 3-amino-2-hydroxy-1-propanesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid, and pharmaceutically acceptable salts thereof.

37. A method for inhibiting IAPP-associated amyloid deposits in a subject, comprising administering to said subject an effective amount of an IAPP-inhibiting compound, or a pharmaceutically acceptable salt thereof, such that said IAPP-associated amyloid deposits are inhibited.

38. The method of claim 37, wherein said IAPP inhibiting compound is selected from the group consisting of 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; DL-2-amino-5-phosphovaleric acid; 4-Phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine; cyclohexylsulfamic acid; *O*-phospho-*L*-serine; 8-methoxyquinoline-5-sulfonic acid; 3-amino-2-hydroxy-1-propanesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid, and pharmaceutically acceptable salts thereof.

39. A method for inhibiting IAPP fibrillogenesis in a subject, comprising administering to said subject an effective amount of an IAPP inhibiting compound, or a pharmaceutically acceptable salt thereof, such that IAPP fibrillogenesis is inhibited.

40. The method of claim 39, wherein said IAPP inhibiting compound has the formula:



wherein

- R^1 and R^2 are each independently a hydrogen atom or a substituted

or unsubstituted aliphatic or aryl group;

- Z and Q are each independently a carbonyl (C=O), thiocarbonyl (C=S), sulfonyl (SO_2), or sulfoxide (S=O);

- k and m are 0 or 1, provided when k is 1, R^1 is not a hydrogen atom and when m is 1, R^2 is not a hydrogen atom;

- p and s are each independently positive integers selected such that the biodistribution of the therapeutic compound for an intended target site is not prevented while maintaining activity of the therapeutic compound;

- T is a linking group; and

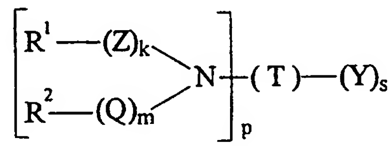
- Y is a group of the formula -AX wherein A is an anionic group at physiological pH, and X is a cationic group.

41. The method of claim 39, wherein said IAPP inhibiting compound is selected from the group consisting of 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; DL-2-amino-5-phosphovaleric acid; 4-Phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine; cyclohexylsulfamic acid; *O*-phospho-*L*-serine; 8-methoxyquinoline-5-sulfonic acid; 3-amino-2-hydroxy-1-propanesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid, and pharmaceutically acceptable salts thereof.

42. A method for reducing IAPP-associated amyloid aggregates in a subject having IAPP-associated amyloid aggregates, the method comprising administering to said subject an effective amount of an IAPP inhibiting compound, or a pharmaceutically acceptable salt thereof, such that said IAPP-associated amyloid aggregates are inhibited.

43. The method of claim 40, wherein said IAPP inhibiting compound is selected from the group consisting of 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; DL-2-amino-5-phosphovaleric acid; 4-Phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine; cyclohexylsulfamic acid; *O*-phospho-*L*-serine; 8-methoxyquinoline-5-sulfonic acid; 3-amino-2-hydroxy-1-propanesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid, and pharmaceutically acceptable salts thereof.

44. A method of modulating amyloid-associated damage to cells, comprising the step of administering *in vivo* or *ex vivo* a composition having the formula



wherein

- R^1 and R^2 are each independently a hydrogen atom or a substituted or unsubstituted aliphatic or aryl group;
- Z and Q are each independently a carbonyl (C=O), thiocarbonyl (C=S), sulfonyl (SO_2), or sulfoxide (S=O);
- k and m are 0 or 1, provided when k is 1, R^1 is not a hydrogen atom and when m is 1, R^2 is not a hydrogen atom;
- p and s are each independently positive integers selected such that the biodistribution of the therapeutic compound for an intended target site is not prevented while maintaining activity of the therapeutic compound;
- T is a linking group; and
- Y is a group of the formula -A X wherein A is an anionic group at physiological pH, and X is a cationic group, in an amount sufficient to modulating amyloid-associated damage to neural cells, such that amyloid-associated damage to neural cells is modulated.

45. The method of claim 44, wherein at least one of k or m equals 1.

46. The method of claim 45, wherein R^1 is an alkyl, alkenyl, or aryl group, k is one, Z is a carbonyl group, R^2 is a hydrogen atom or an alkyl group, m is zero, p and s are 1, T is an alkylene group, and A is SO_3^-.

47. The method of claim 46, wherein said compound is selected from the group consisting of 3-acetylaminopropanesulfonic acid, 3-benzoylamino-1-propanesulfonic acid, and 2-acrylamido-2-methyl-1-propanesulfonic acid.

48. The method of claim 44, wherein R^1 and R^2 are each independently an alkyl, alkenyl, or aryl group, or R^1 and R^2 are taken together to form an alkylene

group, k and m are each one, Z and Q are each independently a carbonyl or a sulfonyl group, p and s are 1, T is an alkylene group, and A is SO_3^-.

49. The method of claim 48, wherein said compound is selected from the group consisting of 3-phthalimido-1-propanesulfonic acid, N-(3-sulfopropyl) saccharin, and 4-phthalimido-1-butanesulfonic acid.

50. The method of claim 44, wherein R^1 is a hydrogen, an alkyl, an alkenyl, or an aryl group, k and m are zero, R^2 is hydrogen or an alkyl group, p and s are each one, T is an alkylene group, and A is SO_3^-.

51. The method of claim 50, wherein said compound is selected from the group consisting of 3-phenylamino-1-propanesulfonic acid sodium salt, 3-(4-pyridylamino)]-1-propanesulfonic acid, 3-(benzylamino)-1-propanesulfonic acid, diethylphosphonoacetic acid, phosphonoformic acid, trisodium salt, 3-benzoylaminopropanesulfonic acid, 2-deoxy-2-(3-sulfopropyl)amino-D-glucose, 1-phenyl-2,3,-dimethyl-4-methylamino-pyrazolon-5-*N*-methylsulfonic acid, 3-[(-3,4-dimethyl-1-adamantyl)-amino]-1-propanesulfonic acid, 3-(2-hydroxyethyl)amino-1-propanesulfonic acid, 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid, (-)-3-[(*R*)-2-hydroxy-1-propyl]amino-1-propanesulfonic acid, 3-[(*d,l*)-2-hydroxy-1-propyl]-1-propanesulfonic acid, 3-(4-hydroxy-1-butyl)amino-1-propanesulfonic acid, 3-(5-hydrox-1-pentyl)amino-1-propanesulfonic acid, 3-(6-hydroxy-1-hexyl)amino-1-propanesulfonic acid, 3-(4-hydroxyphenyl)amino-1-propanesulfonic acid, (+)-3-[(*S*)-2-hydroxy-1-propyl]amino-1-propanesulfonic acid, (+)-3-[(*S*)-1-hydroxy-2-propyl]amino-1-propanesulfonic acid, (-)-3-[(*R*)-1-hydroxy-2-propyl]amino-1-propanesulfonic acid, (+)-3-[(*S*)-1-hydroxy-2-butyl]amino-1-propanesulfonic acid, (-)-3-[(*R*)-1-hydroxy-2-butyl]amino-1-propanesulfonic acid, 3-[(*dl*)-5-Hydroxy-2-pentyl]amino-1-propanesulfonic acid, 3-[(*dl*)-6-hydroxy-2-hexyl]amino-1-propanesulfonic acid, 3-amylamino-1-propanesulfonic acid, 3-hexylamino-1-propanesulfonic acid, 3-heptylamino-1-propanesulfonic acid, 3-octylamino-1-propanesulfonic acid, 3-nonylamino-1-propanesulfonic acid, 3-decylamino-1-propanesulfonic acid, 3-undecylamino-1-propanesulfonic acid, 3-

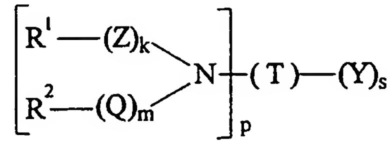
dodecylamino-1-propanesulfonic acid, 3-tridecylamino-1-propanesulfonic acid, 3-tetradecylamino-1-propanesulfonic acid, 3-hexadecylamino-1-propanesulfonic acid, 3-octadecylamino-1-propanesulfonic acid, dimethyl(3-sulfopropyl)-tetradecylammonium hydroxide, inner salt, and 2-(3-Sulfobutyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-b] indole, sodium salt.

52. The method of claim 44, wherein R^1 and R^2 are each independently an alkyl, alkenyl, or aryl group, or $R^1$and R^2 are taken together to form an alkylene group, k and m are zero, p and s are each one, T is an alkylene group, and A is SO_3^-.

53. The method of claim 52, wherein said compound is selected from the group consisting of 3-dimethylamino-1-propanesulfonic acid, 4-(1-piperidinyl)-1-ethanesulfonic acid, 3-[1-(1,2,3,6-tetrahydropyridyl)]-1-propanesulfonic acid, 3-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-[2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-[1-(1,2,3,4-tetrahydroquinolinyl)]-1-propanesulfonic acid, 2-(3-sulfopropyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole, sodium salt, 3-(1-indolinyl)-1-propanesulfonic acid, 1-(3-sulfopropyl)-(*S*)-nicotinium hydroxide inner salt, 3-[2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-(2-isoindolinyl)-1-propanesulfonic acid, 3-(4-benzyl-1-piperidinyl)-1-propanesulfonic acid, 3-[2-(1,2,3,4,5,6,7,8-octahydroisoquinolinyl)]-1-propanesulfonic acid, Thiazol Yellow G, 3-sulfonylmethylphenylalanine, Chicago Sky Blue 6B, 4-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-1-butanesulfonic acid, and 3-Sulfomethyl-L-phenylalanine.

54. The method of claim 44, wherein said compound is selected from the group consisting of 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; DL-2-amino-5-phosphovaleric acid; 4-Phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine; cyclohexylsulfamic acid; *O*-phospho-*L*-serine; 8-methoxyquinoline-5-sulfonic acid; 3-amino-2-hydroxy-1-propanesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid, and pharmaceutically acceptable salts thereof.

55. A method of modulating secondary amyloidosis *in vivo* or *ex vivo*, comprising the step of administering *in vivo* or *ex vivo* a composition having the formula



wherein

- R^1 and R^2 are each independently a hydrogen atom or a substituted or unsubstituted aliphatic or aryl group;
- Z and Q are each independently a carbonyl (C=O), thiocarbonyl (C=S), sulfonyl (SO_2), or sulfoxide (S=O);
- k and m are 0 or 1, provided when k is 1, R^1 is not a hydrogen atom and when m is 1, R^2 is not a hydrogen atom;
- p and s are each independently positive integers selected such that the biodistribution of the therapeutic compound for an intended target site is not prevented while maintaining activity of the therapeutic compound;
- T is a linking group; and
- Y is a group of the formula -A X wherein A is an anionic group at physiological pH, and X is a cationic group, in an amount sufficient to modulating amyloid-associated damage to neural cells, such that amyloid-associated damage to neural cells is modulated.

56. The method of claim 55, wherein at least one of k or m equals 1.

57. The method of claim 56, wherein R^1 is an alkyl, alkenyl, or aryl group, k is one, Z is a carbonyl group, R^2 is a hydrogen atom or an alkyl group, m is zero, p and s are 1, T is an alkylene group, and A is SO_3^-.

58. The method of claim 57, wherein said compound is selected from the group consisting of 3-acetylaminopropanesulfonic acid, 3-benzoylamino-1-propanesulfonic acid, and 2-acrylamido-2-methyl-1-propanesulfonic acid.

59. The method of claim 58, wherein R^1 and R^2 are each independently an alkyl, alkenyl, or aryl group, or R^1 and R^2 are taken together to form an alkylene

group, k and m are each one, Z and Q are each independently a carbonyl or a sulfonyl group, p and s are 1, T is an alkylene group, and A is SO_3^-.

60. The method of claim 59, wherein said compound is selected from the group consisting of 3-phthalimido-1-propanesulfonic acid, N-(3-sulfopropyl) saccharin, and 4-phthalimido-1-butanesulfonic acid.

61. The method of claim 55, wherein R^1 is a hydrogen, an alkyl, an alkenyl, or an aryl group, k and m are zero, R^2 is hydrogen or an alkyl group, p and s are each one, T is an alkylene group, and A is SO_3^-.

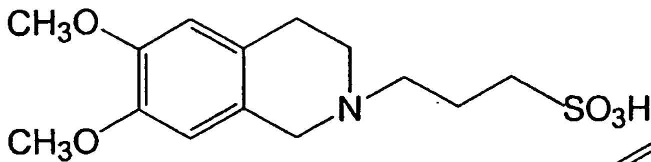
62. The method of claim 61, wherein said compound is selected from the group consisting of 3-phenylamino-1-propanesulfonic acid sodium salt, 3-(4-pyridylamino)]-1-propanesulfonic acid, 3-(benzylamino)-1-propanesulfonic acid, diethylphosphonoacetic acid, phosphonoformic acid, trisodium salt, 3-benzoylaminopropanesulfonic acid, 2-deoxy-2-(3-sulfopropyl)amino-D-glucose, 1-phenyl-2,3,-dimethyl-4-methylamino-pyrazolon-5-*N*-methylsulfonic acid, 3-[(-3,4-dimethyl-1-adamantyl)-amino]-1-propanesulfonic acid, 3-(2-hydroxyethyl)amino-1-propanesulfonic acid, 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid, (-)-3-[(*R*)-2-hydroxy-1-propyl]amino-1-propanesulfonic acid, 3-[(*d,l*)-2-hydroxy-1-propyl]-1-propanesulfonic acid, 3-(4-hydroxy-1-butyl)amino-1-propanesulfonic acid, 3-(5-hydrox-1-pentyl)amino-1-propanesulfonic acid, 3-(6-hydroxy-1-hexyl)amino-1-propanesulfonic acid, 3-(4-hydroxyphenyl)amino-1-propanesulfonic acid, (+)-3-[(*S*)-2-hydroxy-1-propyl]amino-1-propanesulfonic acid, (+)-3-[(*S*)-1-hydroxy-2-propyl]amino-1-propanesulfonic acid, (-)-3-[(*R*)-1-hydroxy-2-propyl]amino-1-propanesulfonic acid, (+)-3-[(*S*)-1-hydroxy-2-butyl]amino-1-propanesulfonic acid, (-)-3-[(*R*)-1-hydroxy-2-butyl]amino-1-propanesulfonic acid, 3-[(*dl*)-5-Hydroxy-2-pentyl]amino-1-propanesulfonic acid, 3-[(*dl*)-6-hydroxy-2-hexyl]amino-1-propanesulfonic acid, 3-amylamino-1-propanesulfonic acid, 3-hexylamino-1-propanesulfonic acid, 3-heptylamino-1-propanesulfonic acid, 3-octylamino-1-propanesulfonic acid, 3-nonylamino-1-propanesulfonic acid, 3-decylamino-1-propanesulfonic acid, 3-undecylamino-1-propanesulfonic acid, 3-

dodecylamino-1-propanesulfonic acid, 3-tridecylamino-1-propanesulfonic acid, 3-tetradecylamino-1-propanesulfonic acid, 3-hexadecylamino-1-propanesulfonic acid, 3-octadecylamino-1-propanesulfonic acid, dimethyl(3-sulfopropyl)-tetradecylammonium hydroxide, inner salt, and 2-(3-Sulfobutyl)-1,2,3,4-tetrahydro-9H-pyrido [3,4-b] indole, sodium salt.

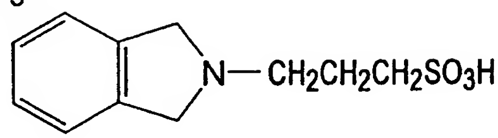
63. The method of claim 55, wherein R^1 and R^2 are each independently an alkyl, alkenyl, or aryl group, or $R^1$and R^2 are taken together to form an alkylene group, k and m are zero, p and s are each one, T is an alkylene group, and A is SO_3^-.

64. The method of claim 63, wherein said compound is selected from the group consisting of 3-dimethylamino-1-propanesulfonic acid, 4-(1-piperidinyl)-1-ethanesulfonic acid, 3-[1-(1,2,3,6-tetrahydropyridyl)]-1-propanesulfonic acid, 3-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-[2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-[1-(1,2,3,4-tetrahydroquinolinyl)]-1-propanesulfonic acid, 2-(3-sulfopropyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole, sodium salt, 3-(1-indolinyl)-1-propanesulfonic acid, 1-(3-sulfopropyl)-(*S*)-nicotinium hydroxide inner salt, 3-[2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinyl)]-1-propanesulfonic acid, 3-(2-isoindolinyl)-1-propanesulfonic acid, 3-(4-benzyl-1-piperidinyl)-1-propanesulfonic acid, 3-[2-(1,2,3,4,5,6,7,8-octahydroisoquinolinyl)]-1-propanesulfonic acid, Thiazol Yellow G, 3-sulfonylmethylphenylalanine, Chicago Sky Blue 6B, 4-[2-(1,2,3,4-tetrahydroisoquinolinyl)]-1-butanesulfonic acid, and 3-Sulfomethyl-L-phenylalanine.

65. The method of claim 55, wherein said compound is selected from the group consisting of 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; DL-2-amino-5-phosphovaleric acid; 4-Phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine; cyclohexylsulfamic acid; *O*-phospho-*L*-serine; 8-methoxyquinoline-5-sulfonic acid; 3-amino-2-hydroxy-1-propanesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid, and pharmaceutically acceptable salts thereof.



I



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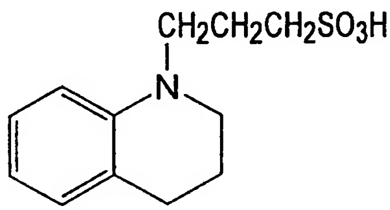
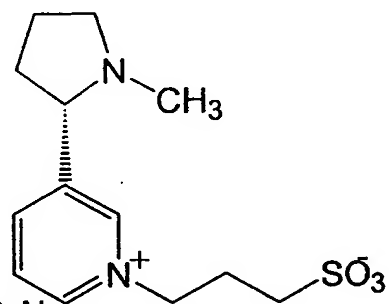


III



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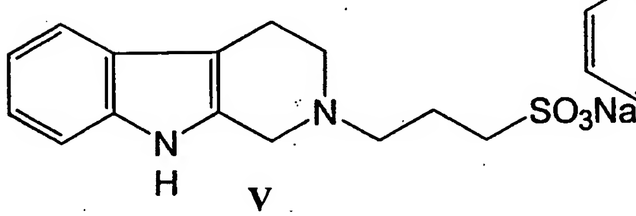
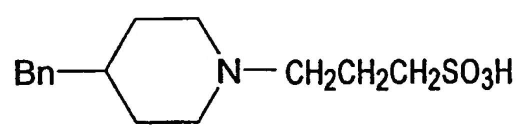
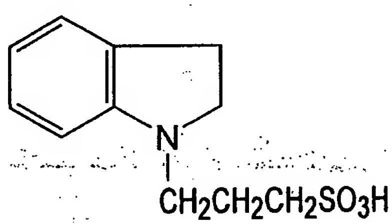


V



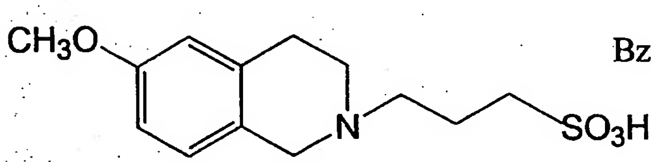
VI



VII

$AcNHCH_2CH_2CH_2SO_3Na$

VIII

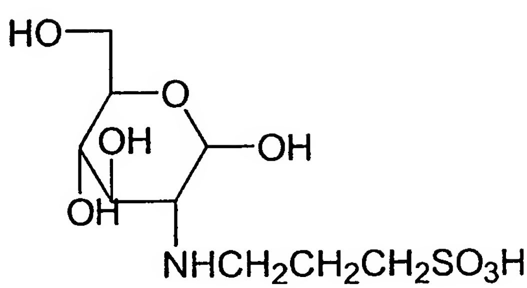


IX

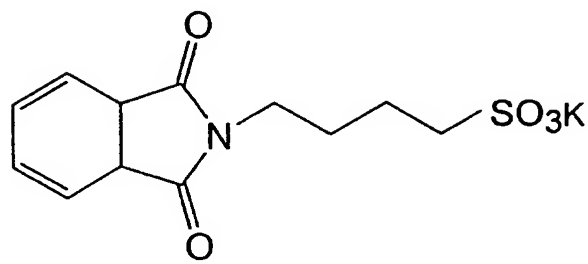
$BzNHCH_2CH_2CH_2SO_3Na$

X

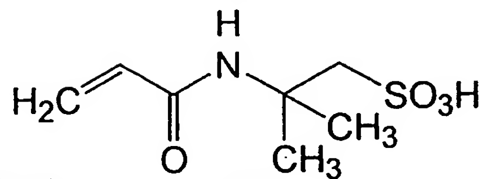
FIG. 1



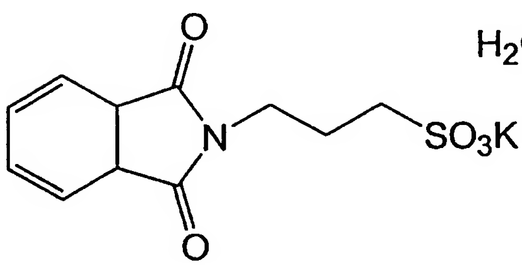
XX



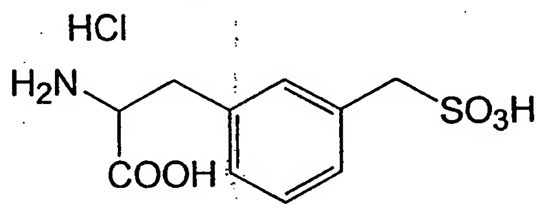
XIX



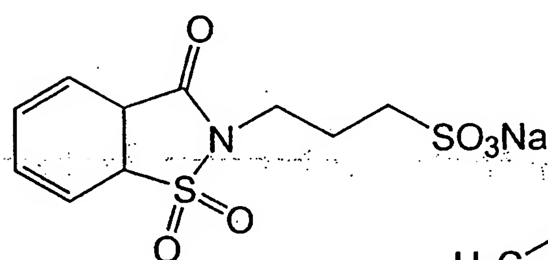
XXI



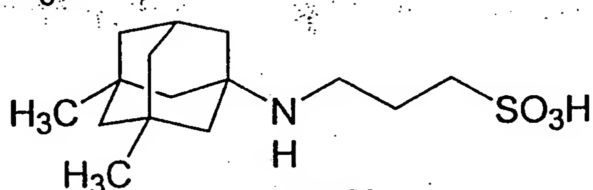
XXIII



XXII

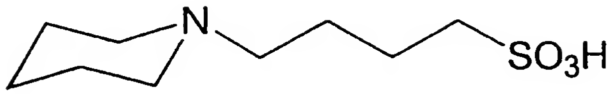


XXV



XXIV

FIG. 2



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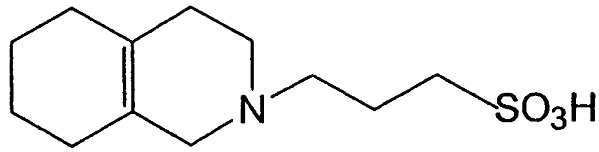

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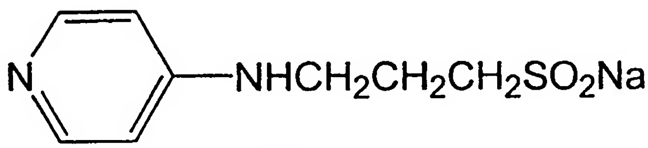

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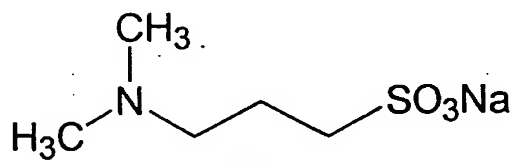

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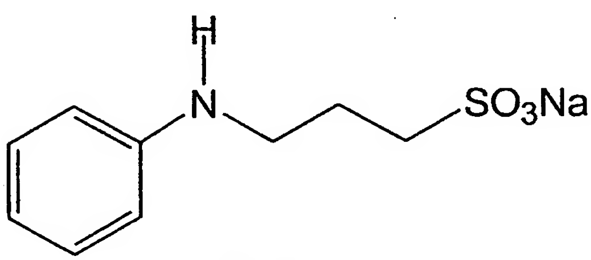

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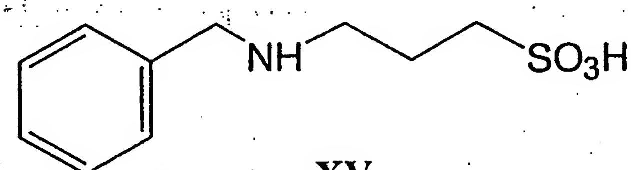
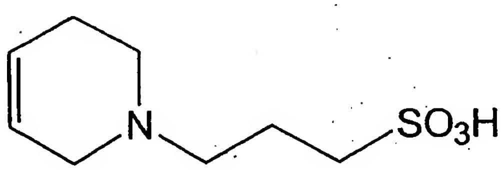


XV



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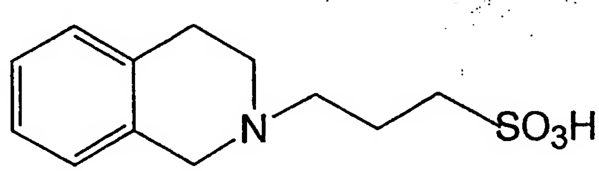
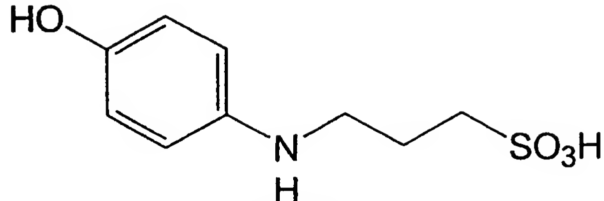
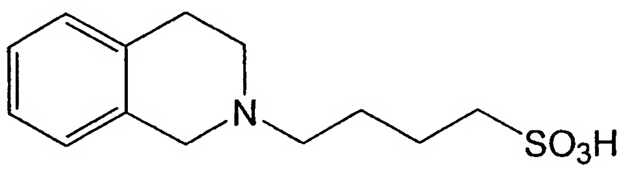


XVII

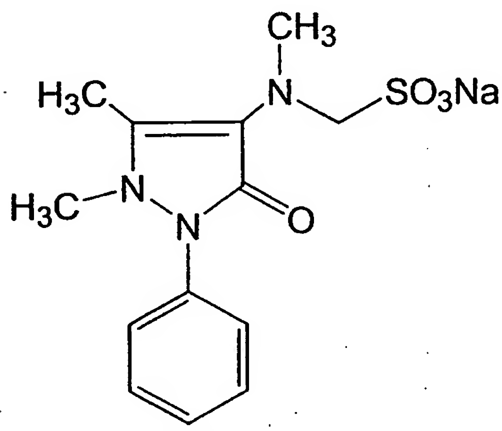
FIG. 3



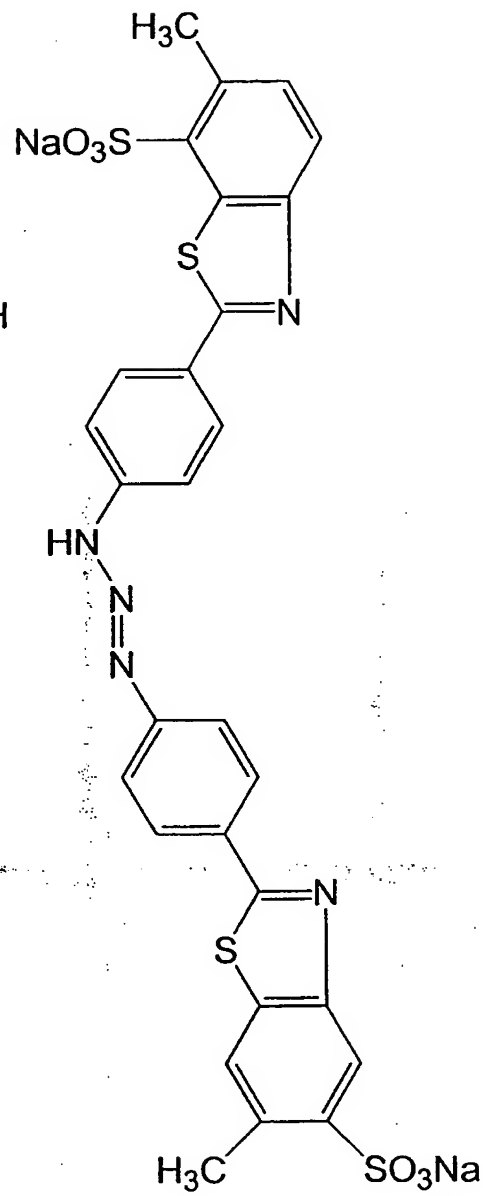
XXXV



XXVI

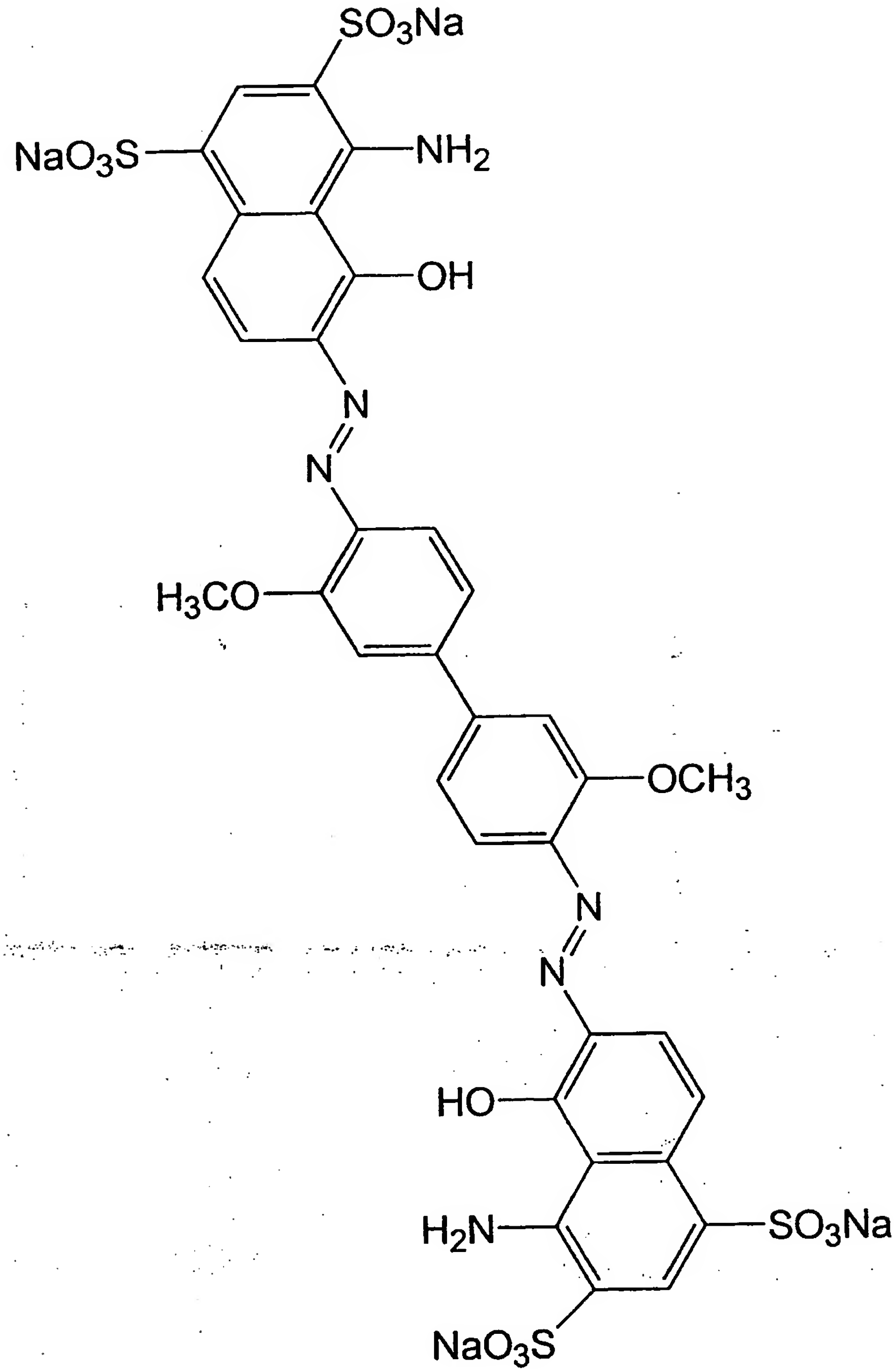


XXVII



XXVIII

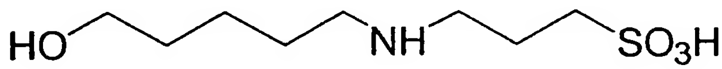
FIG. 4



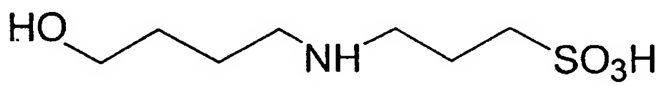
XXIX

FIG. 5

XXXIII



XXXI



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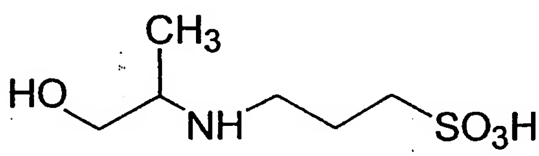

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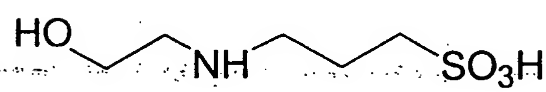
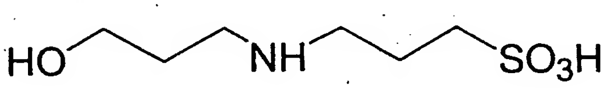
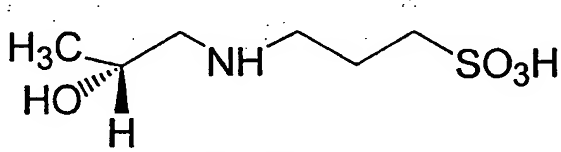


XXX

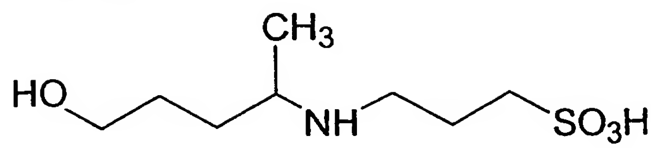


XXXII



XXXIV

FIG. 6



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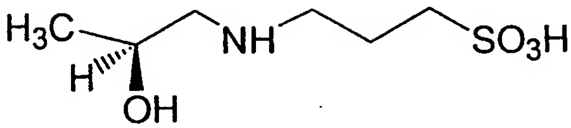

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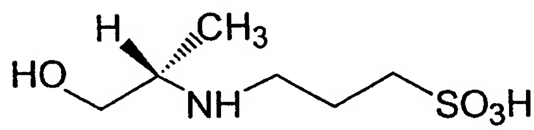

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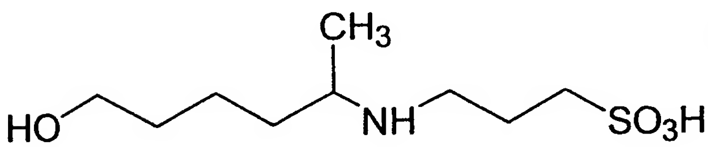
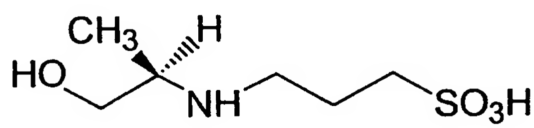
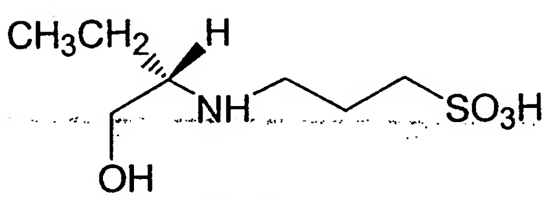


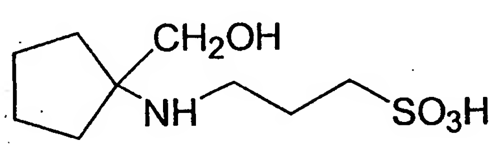
XLI



XL



XLIII



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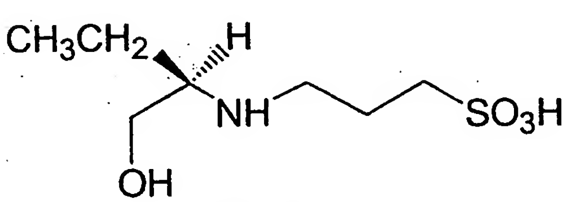


XLIV

FIG. 7

$CH_3(CH_2)_4NHCH_2CH_2CH_2SO_3H$

XLV

$CH_3(CH_2)_5NHCH_2CH_2CH_2SO_3H$

XLVI

$CH_3(CH_2)_6NHCH_2CH_2CH_2SO_3H$

XLVII

$CH_3(CH_2)_7NHCH_2CH_2CH_2SO_3H$

XLVIII

$CH_3(CH_2)_8NHCH_2CH_2CH_2SO_3H$

L

$CH_3(CH_2)_9NHCH_2CH_2CH_2SO_3H$

LI

$CH_3(CH_2)_{10}NHCH_2CH_2CH_2SO_3H$

LII

$CH_3(CH_2)_{11}NHCH_2CH_2CH_2SO_3H$

LIII

$CH_3(CH_2)_{12}NHCH_2CH_2CH_2SO_3H$

LIV

$CH_3(CH_2)_{13}NHCH_2CH_2CH_2SO_3H$

LV

$CH_3(CH_2)_{15}NHCH_2CH_2CH_2SO_3H$

LVI

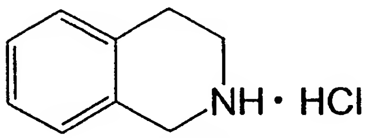
$CH_3(CH_2)_{17}NHCH_2CH_2CH_2SO_3H$

LVII

FIG. 8

$OH_2\overset{NH_2}{C}CHCH_2CH_2CH_2PO_3H_2$

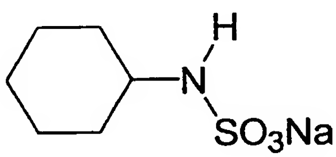
LVIII



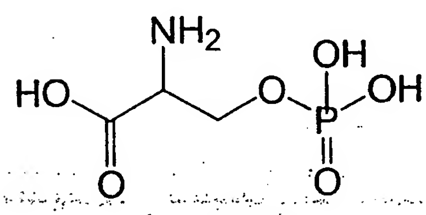
LVIX

$OHCH_2CH_2CH_2NHCH_2CH_2CH_2SO_3H$

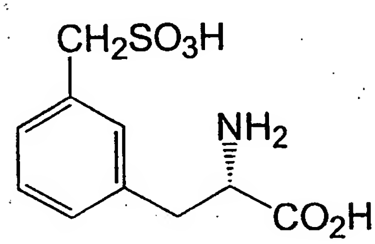
LVX



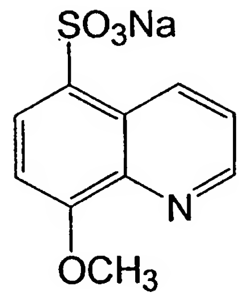
LVXI



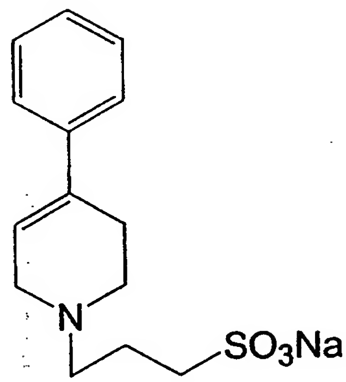
LVXII



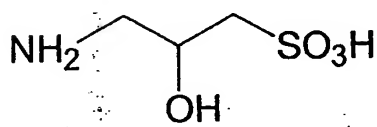
LVXIII



LVXIV



LVXV



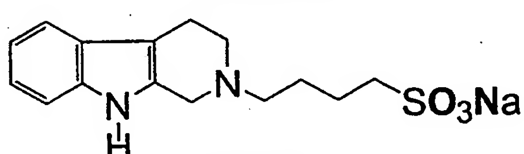
LVXVI

$(CH_3)_2NCH_2CH_2CH_2SO_3H$

LVXVII

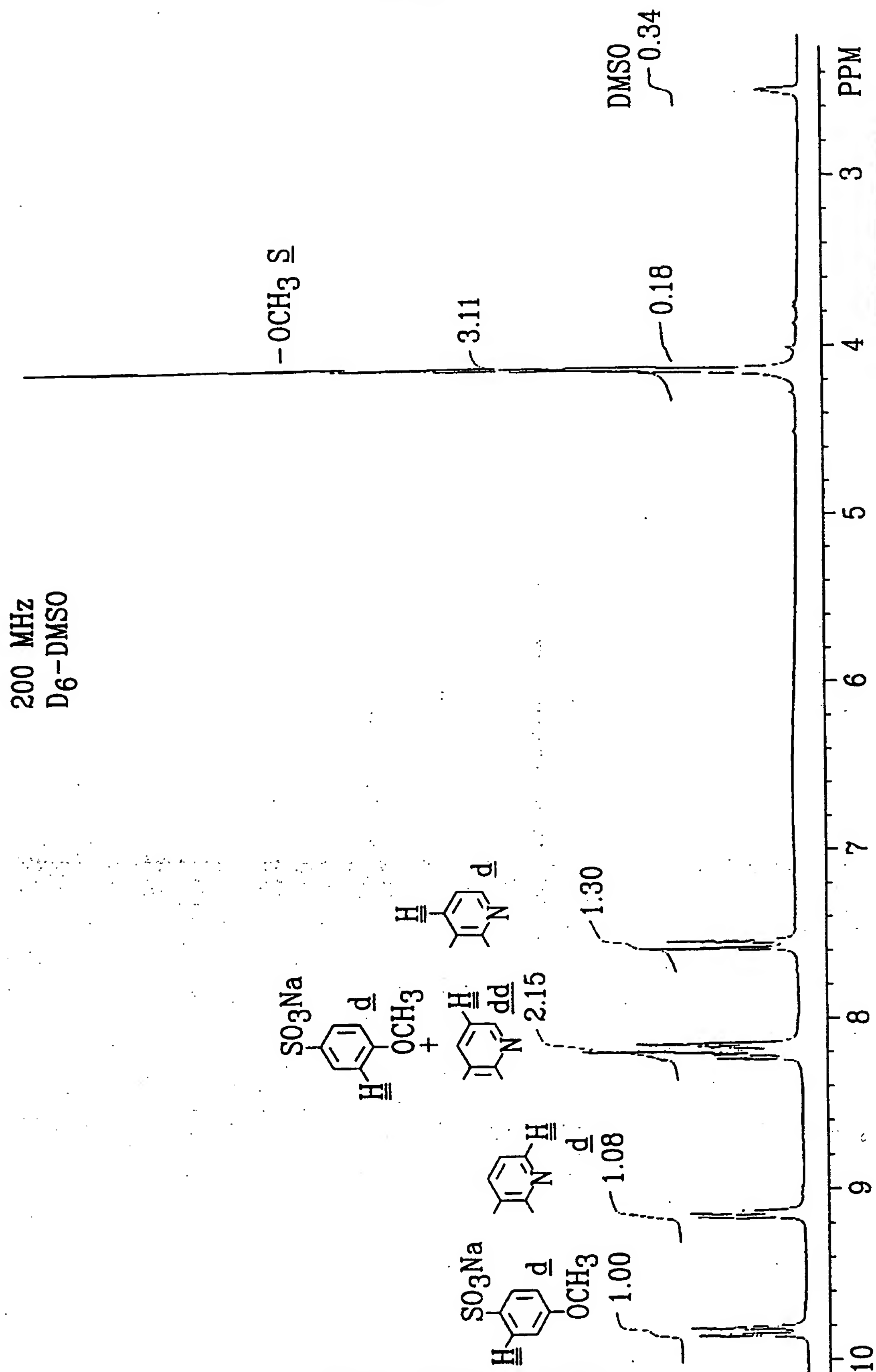
$CH_3(CH_2)_{13}N^+(CH_3)_2[(CH_2)_3SO_3]$

LVXVIII



LVXIX

FIG. 9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D6-DMSO
DMSO
0.34
-OCH3 s
3.11
0.18
1.30
2.15
1.08
1.00
SO3Na
OCH3
d
dd
PPM
3
4
5
6
7
8
9
10

FIG. 10

11/12

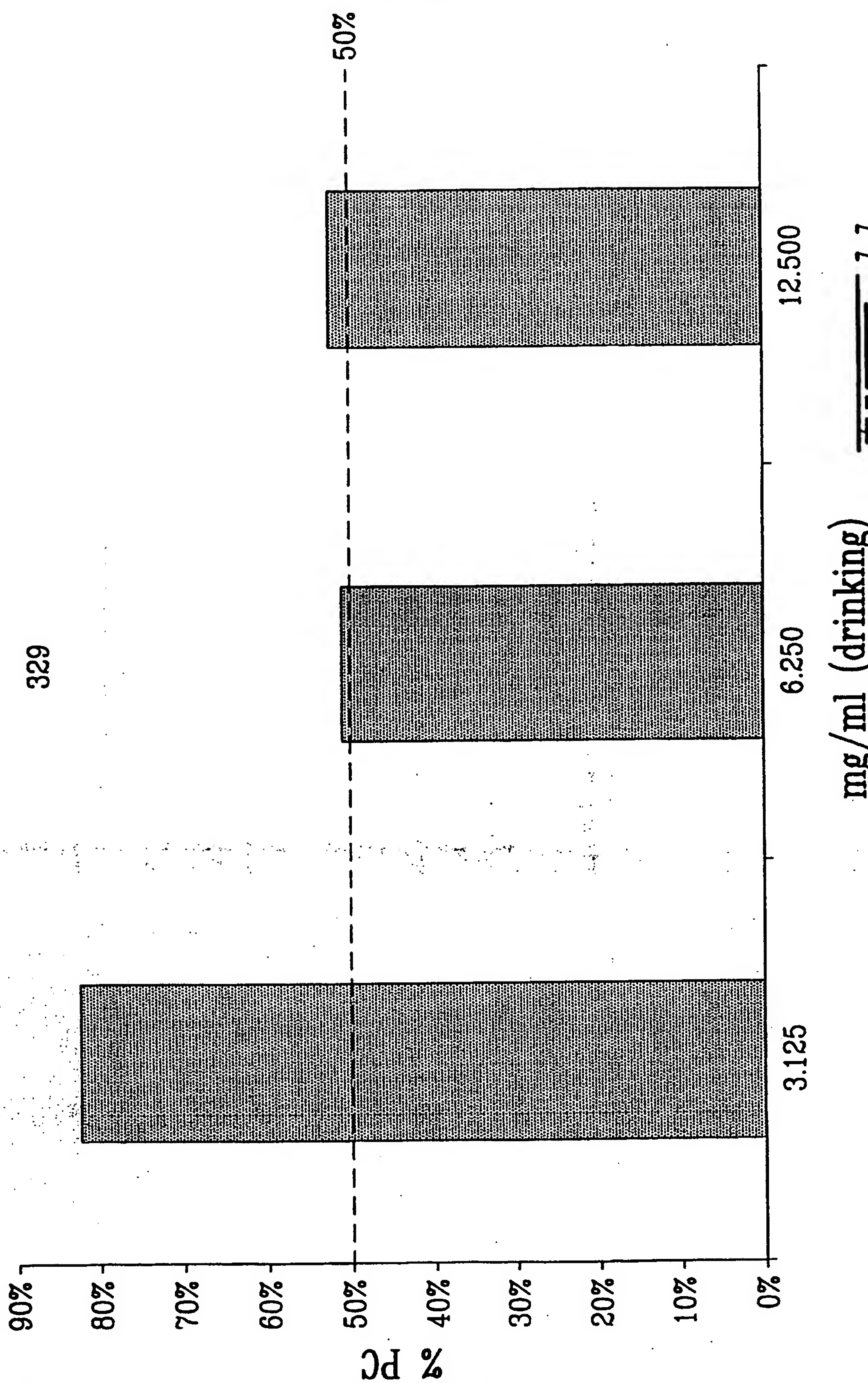
50%
329
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
% PC
3.125
6.250
12.500
mg/ml (drinking)

FIG. 11

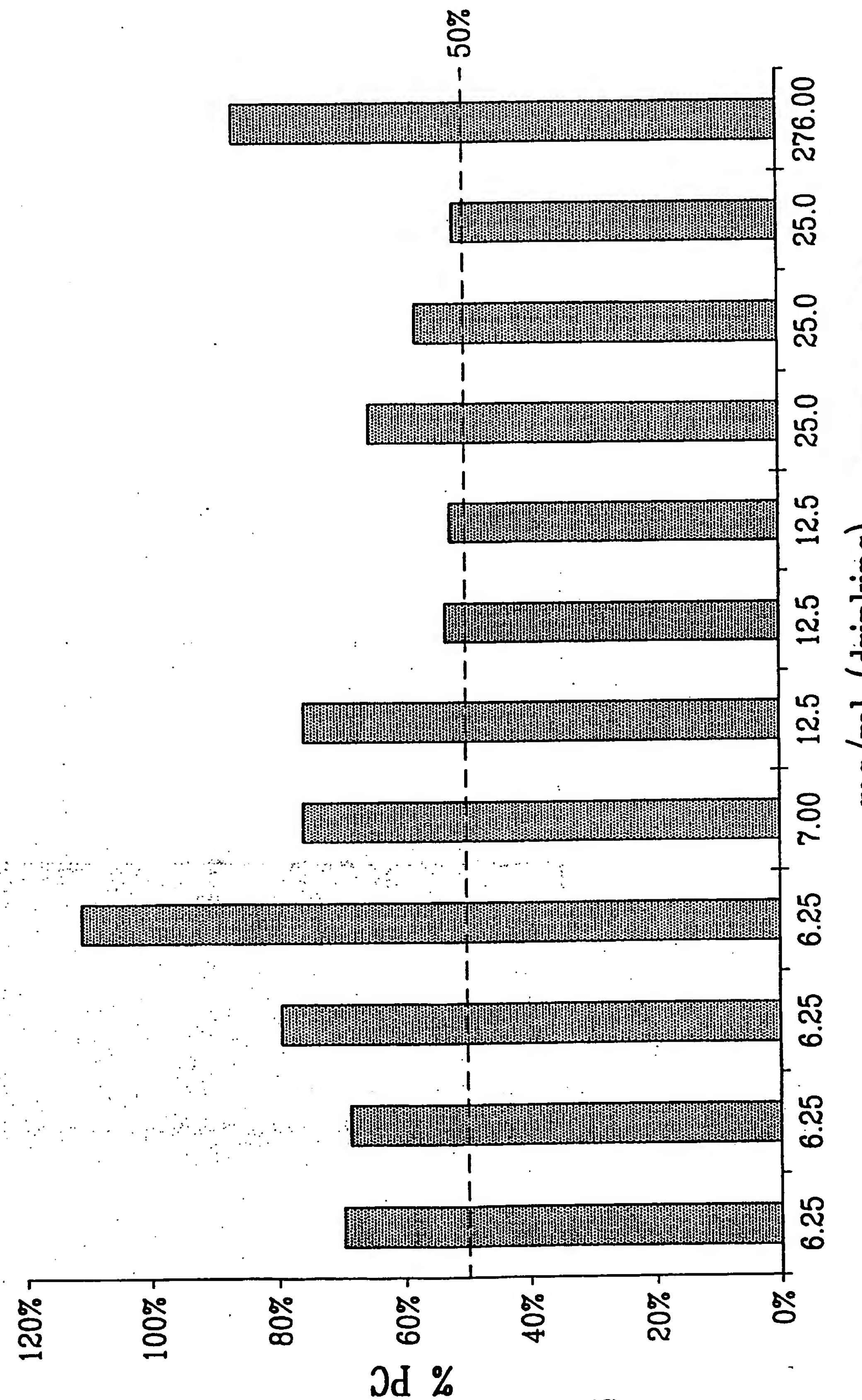
50%
% PC
120%
100%
80%
60%
40%
20%
0%
6.25
6.25
6.25
6.25
7.00
12.5
12.5
12.5
25.0
25.0
25.0
276.00
mg/ml (drinking)

FIG-12